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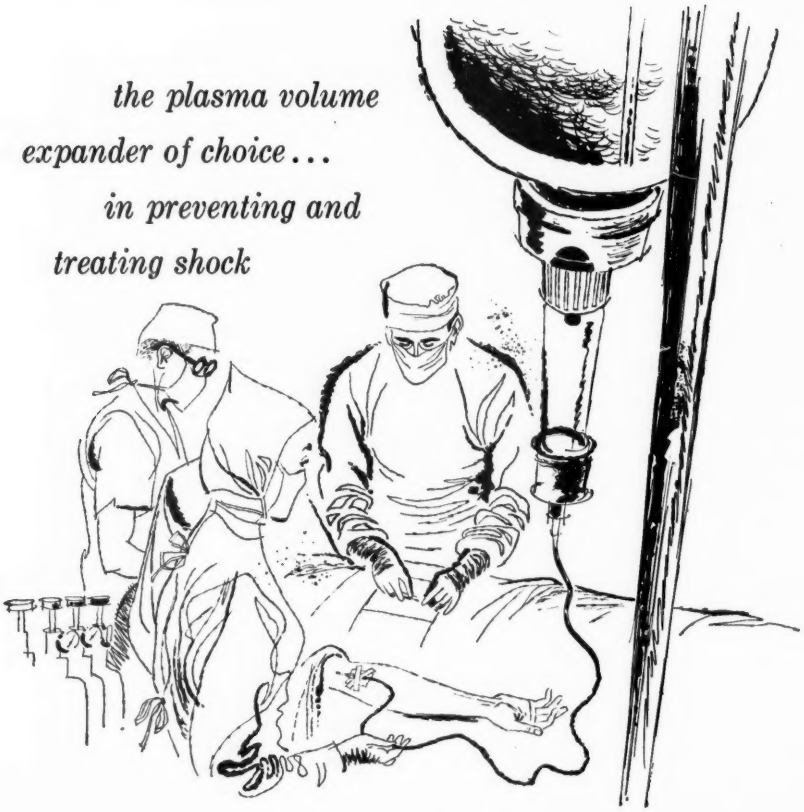

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SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 98 JUNE, 1954 NUMBER 6

FAT EMBOLISM

A Clinical and Experimental Study of Mechanisms Involved

ROY L. SWANK, M.D., Portland, Oregon, and
GORDON S. DUGGER, M.D., Chapel Hill, North Carolina

In recent years we have become increasingly aware of patients with cerebral fat embolism occurring early after injury and without pulmonary symptoms. These patients may have cerebral concussion, complicating fractures, or large area body mutilations and may recover consciousness in a relatively short time, only to become stuporous again in a few hours. The entire course of these events may take no longer than 6 to 12 hours. These patients subsequently recover, or may die in 24 to 48 hours. Gross brain lesions are frequently absent at postmortem examination, but in some cases fat emboli, particularly in the brain and lungs, can be demonstrated. In other cases, the symptoms and signs of cerebral damage due to fat embolism occur after fractures or injuries repaired by operative procedures under anesthesia. The frequent occurrence, and the importance of early recognition of fat embolism in which the signs of cerebral embolism occur soon after fracture and prior to the development of signs of pulmonary embolism are generally overlooked, but recent publications by Kershman and Haddad, Schneider, and Alldred, indicate that awareness of this problem is increasing.

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

Supported jointly by grants from the Multiple Sclerosis Society of Canada and from the Department of Health and Welfare, Ottawa, Canada.

The following 2 cases exemplify the problem of fat embolism as we have seen it.

Case 1. K.L., a 5 year old boy, had been struck by a motor vehicle at 10:15 a.m. on December 24, 1952, and had been taken immediately to the hospital. He had not lost consciousness and there were no external signs of injury. The abdomen was tender and rigid, and the neurologic examination was entirely negative. An upright x-ray film of the abdomen showed free air in the peritoneal cavity. A laparotomy revealed a large tear in the stomach; the other abdominal viscera were normal. He recovered promptly from the operation and remained alert and rational for 5 hours. At 4:15 p.m. he began to have nystagmus and within a few minutes he became irrational and finally unconscious. The temperature rose to 106.2 degrees and the blood pressure fell to 60 systolic. At about the same time the eyes deviated to the right and the pupils became dilated and failed to react to light. A Babinski sign appeared on the left and the deep tendon jerks no longer could be obtained. After transfusion of whole blood and a lumbar puncture which showed bloody spinal fluid he was transferred to the Montreal Neurological Institute at 8:00 p.m., December 24, 1952. Upon admission he was deeply comatose and in shock. He was having two kinds of attacks. The first of these consisted of episodes of intense bilateral rigidity with opisthotonos, initiated and increased by cutaneous stimulation. The other attacks were focal cerebral seizures which were chiefly left-sided. Roentgenograms of the skull, chest, and pelvis were normal. A hemoglobin determination upon admission was 17 grams per 100 milliliters, and a hematocrit 3 hours after admission was 46 per cent. There was no fat in the urine, but microscopic examination of the plasma with contrast light showed many large fat droplets. The patient was given whole blood

transfusions and oxygen, but the blood pressure remained at shock levels. During the entire period of hospitalization there was no production of urine. Convulsions occurred frequently and were controlled with difficulty. It became impossible to maintain the patient's blood pressure. Respirations stopped 11 hours after admission to the Montreal Neurological Institute and approximately 19 hours after the injury.

Pathology. At autopsy there was an extensive retroperitoneal hemorrhage with injury to the surrounding soft tissues and fat deposits. The lungs were edematous and hyperemic. The brain showed no gross evidence of injury.

Microscopic examination. Many small hemorrhagic areas were exhibited in the lungs. Sections stained for fat by a modified Marchi method (8) showed globules of fat of various sizes in the pulmonary vessels (Figs. 5 and 6). There were many small particles of fat in the alveoli and some of these had been phagocytized. The most striking feature was the occlusion of many capillaries and arterioles by single fat globules. In the cerebral cortex many vessels had droplets of fat associated with them either in the perivascular spaces, the vessel walls, or the lumina (Figs. 1, 2, 3, and 4). There were many vessels containing in their lumina or having attached to their walls numerous small globules of fat, 2 to 3 micra in diameter. In many instances these had aggregated or clumped together completely occluding the vessel. Fat was found in the perivascular spaces and some of this had been phagocytized. Particles of fat of various sizes were scattered freely throughout the brain substance. The globules of intravascular fat in the cerebral vessels were uniformly much smaller than those observed within the lung.

CASE 2. E.M. was a 21 year old woman, who was injured in an automobile accident 5 days before admission to the Montreal Neurological Institute on April 9, 1953. Immediately after the accident she was deeply unconscious but a few hours later she was able to make purposeful movements in response to pin prick. She had occipital and frontal scalp lacerations. A few hours after the accident cyanosis and dyspnea developed. She was found to have fractures of the right second, and the left fifth and sixth ribs, and a left tension pneumothorax. Respiratory difficulty disappeared after 1,500 cubic centimeters of air had been removed from the left pleural cavity. An x-ray film showed a comminuted fracture of the lower part of the middle third of the left femur. On the day after injury she became less responsive and developed episodes of decerebrate rigidity. She was able to move the right side better than the left. On this same day the fractured right femur was plated as a prophylactic measure against fat emboli. Afterward her condition remained stationary up to the time of transfer. When admitted to the Montreal Neurological Institute 5 days after the accident she was unconscious, restless and cyanotic, and in obvious pulmonary distress. There were many coarse rhonchi throughout the chest, but these cleared and breathing improved after dependent drainage of the chest. She exhibited transient episodes of hypertonia and bilateral Babinski signs. The left lateral ventricle of the brain was punctured through a left posterior parietal hole and blood was aspirated. Her condition remained unchanged until 15 hours after admission when her respirations suddenly became shallow and irregular and she died in a few minutes.

It was recognized that this patient probably had a focal brain injury due to trauma. In addition there were also signs of diffuse brain damage, and it was thought that these possibly were secondary to multiple fat emboli.

Pathology. At autopsy there was a contusion of the lower lobe of the left lung. Over the cerebral hemispheres there was a diffuse thin subarachnoid hemorrhage. When the brain was sectioned the ventricles were found to be slightly dilated and to contain some blood in both posterior horns. In the right anterior thalamus and adjacent parts of the caudate nucleus and putamen there was a hemorrhagic area which appeared to have been formed by the confluence of several smaller hemorrhages. In the depths of some of the sulci scattered small hemorrhages were seen.

Microscopic sections prepared by the modified Marchi technique showed many droplets of fat in the hemorrhagic area of the brain. Some of this was free as droplets, and the rest was contained in macrophages. Many capillaries were filled with particles of fat. In the cerebral cortex there were capillaries and arterioles occluded by single fat globules (Figs. 7 and 8), and many vessels contained aggregates of small fat particles (Fig. 9). Fat was also found in blood vessel walls and in perivascular spaces (Fig. 10). The lungs contained a very large amount of fat and much of this in the alveoli had been ingested by phagocytes (Fig. 13). In many large vessels numerous small fat globules had become confluent to form large globules of fat (Figs. 11 and 12). The kidneys contained a great deal of free fat, and many globules of fat were seen in the glomerular capillary loops.

In the 2 cases just presented the manifestations of fat embolism were primarily cerebral. In the first case progression to death was relatively fast, but in the second case a temporary stabilization, after early cerebral embolism, occurred, and this was later followed by pulmonary distress and manifestations of cerebral involvement and death. These early manifestations of cerebral embolism are frequently overlooked because it is generally held that the clinical manifestations of fat embolism are delayed for 48 to 72 hours and are at first pulmonary. Only after the development of short-

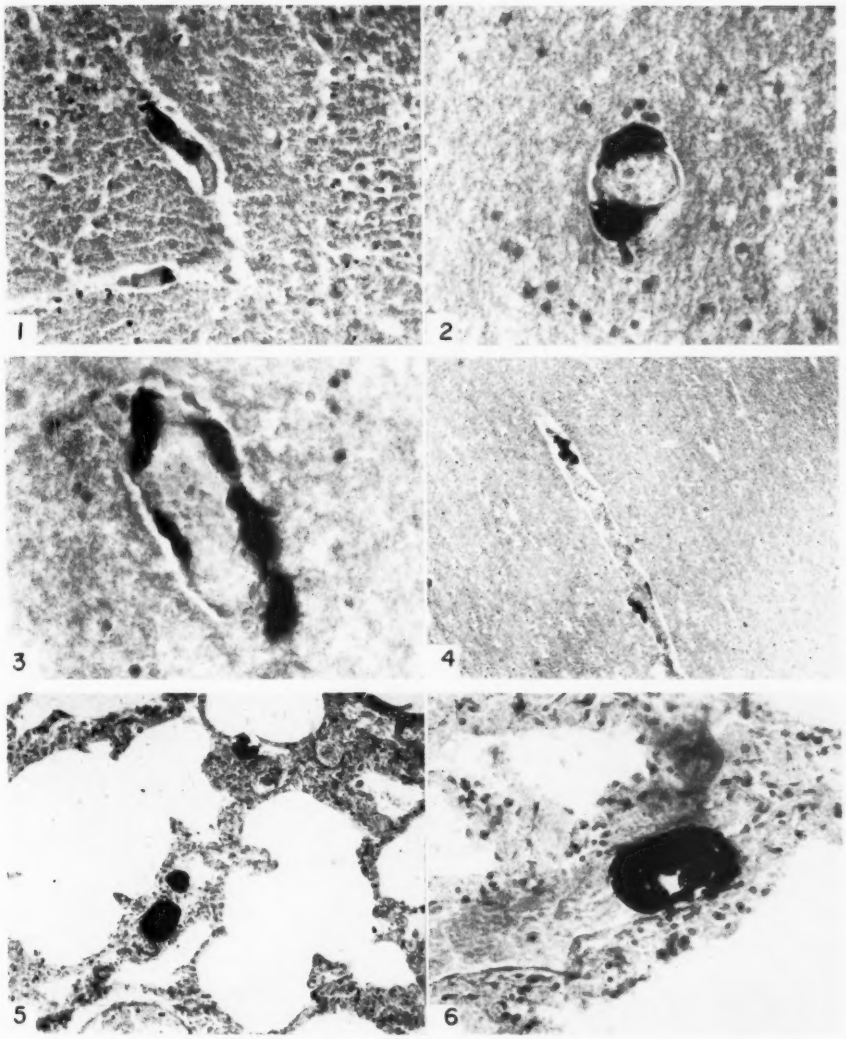

Fig. 1. Fat emboli in small blood vessels in the medulla. Modified Marchi technique (8), counterstained with hematoxylin and van Gieson, ×240.

Fig. 2. Small blood vessel in white matter of cerebral cortex, containing two large fat globules in its wall. Staining as in Figure 1, ×355.

Fig. 3. Blood vessel in white matter with numerous large fat globules in vessel wall. Staining as in Figure 1, ×355.

Fig. 4. Particles of fat along vessel wall in cerebral white matter. Staining as in Figure 1, ×101.

Fig. 5. Fat emboli in pulmonary vessels. Staining as in Figure 1, ×99.

Fig. 6. Large pulmonary vessel containing fat embolus. Staining as in Figure 1, ×240.

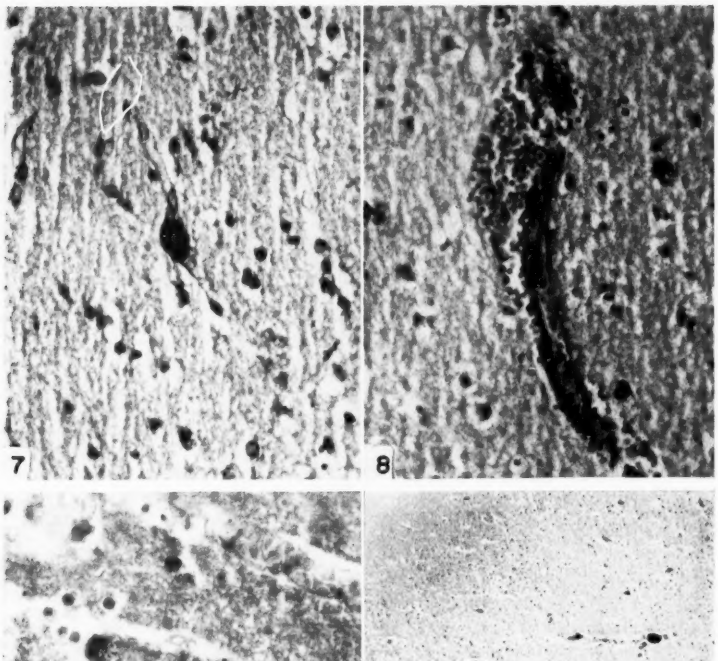

Fig. 7. Case 2. Capillary in cerebral gray matter containing single embolus. Modified Marchi technique (8), counterstained by cresyl violet, ×281.

Fig. 8. Small blood vessel in cerebral gray matter containing fat emboli and surrounded by small hemorrhage. Staining as in Figure 7, ×242.

Fig. 9. Blood vessel in cerebral gray matter occluded by aggregation of many small fat particles. Staining as in Figure 1, ×429.

Fig. 10. Three small blood vessels in medulla containing fat globules in their lumina and walls. Staining as in Figure 1, ×86.

ness of breath, hemorrhagic sputum, and rales at the bases of the lungs is it thought that signs of cerebral embolism, namely excitement, stupor, convulsions, paralyses, and coma, develop.

The study now to be presented is an attempt to explain the early onset of cerebral manifestations in some cases of fat embolism in which major fractures and head concussion or anesthesia coexist and to clarify some of the fac-

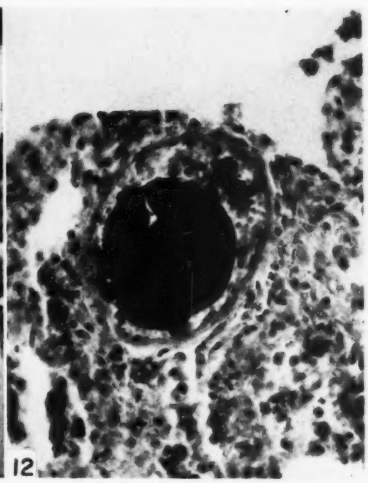

FIG. 11. Case 2. Large fat embolus in a pulmonary artery. Staining as in Figure 7, ×115.

FIG. 12. Pulmonary blood vessel containing large fat globule. Staining as in Figure 7, ×242.

tors involved in the mobilization of the fat forming the emboli.

MATERIAL AND METHODS

Young white rabbits of approximately the same age were used. Most of these were lean and had barely reached their full growth (lean group). A few of these had been permitted to fatten for 3 weeks on fox chow and vegetable greens. These few are referred to as fat rabbits. In one series of lean animals one femur was fractured under light nembutal anesthesia; in a second the thigh muscles on one side were crushed under light nembutal anesthesia. After variable periods they were sacrificed by injection of an overwhelming dose of nembutal. Additional groups of both lean and fat animals were fasted before sacrifice, or before fracture and sacrifice. Six animals (all lean) were sacrificed by exsanguination without anesthesia, and 11 others by exsanguination during deep nembutal anesthesia. All the rest were sacrificed by giving an overwhelming dose of nembutal. In all instances the abdominal and thoracic viscera and then the brain were removed and fixed in formalin.

The brains and lungs were stained for fat by sudan III and by a modified Marchi technique. Only the latter method proved satisfactory for our study. The blocks of tissue were sectioned 10 micra thick and the amount of black osmic stained fat was measured in the following way. For the lungs all visible fat globules in the parenchyma or blood vessels in the lung fields in the area of 4 squares of a grid, each square measuring 3.5 by 3.5 millimicra were counted. This result was then multiplied by 5 to give the total fat globule counts for an area equal to 20 squares of the grid. A magnification of approximately 100 was used (10 times objective and 10 times ocular). For the brain all the visible fat glob-

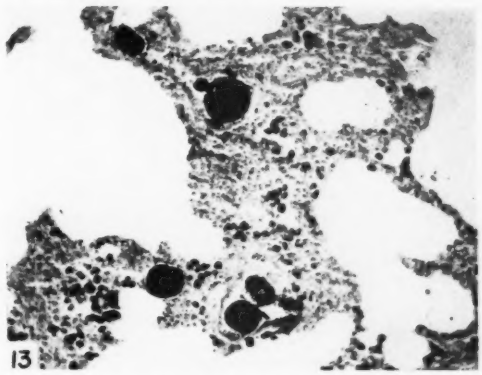

FIG. 13. A number of pulmonary blood vessels containing fat emboli. Staining as in Figure 7, ×86.

TABLE I.—CONTROL STUDIES ON RELATIVE FAT GLOBULE COUNTS

Death by	No.	Lungs	Aver.	Brain					
				Gray matter	Aver.	White matter	Aver.	Total	Aver.
Exsanguination without anesthesia	76	65		16		0		16	
	77	90		21		3		24	
	78	20	45	53	33	6	4	59	37
	79	10		43		5		48	
	80	15		40		4		44	
	81	60		28		3		31	
Deep numbutal anesthesia with exsanguination	40	55		121		9		130	
	44	160		116		8		124	
	45	30	89	101	106	13	10	114	116
	46	60		87		8		95	
	47	140							
Fasted 24 hours. Deep nembutal anesthesia with exsanguination	63	10		30		4		34	
	64	15		52		2		54	
	65	15	13	20	34	2	3	22	37
	60	20							
	61	5							
	62	10							

ules, using the magnification of 100, were determined in the gray and white matter. Corrections were then made for differences in size of the cross section areas of the brain tissue, so that the total area of brain (white plus gray matter) in all instances equalled 20 squares of the grid. Thus the relative numbers of fat globules in comparable areas of the brain and lungs were determined and form the basis of the comparisons to follow.

RESULTS

Location of the fat globules. In the lungs the fat globules were found in the arterioles, capillaries, and in the alveoli. They varied in size from globules barely visible to globules as large as 40 and 50 micra in diameter when much fat was present (Figs. 18 and 19).

In the brains almost all globules of fat were small (up to 5 or 8 micra in diameter) and were found inside the lumen of small blood vessels or in the wall or perivascular tissues of the smaller arterioles and capillaries (Figs. 14, 15, 16, and 17). Very little fat was contained in macrophages.

Control studies. Seemingly small differences in the treatment of the animals altered the fat globule counts in the lungs and the brain. This is shown in Table I which gives the relative fat globule counts in the lungs, and in the gray and white matter of the brain after sacrifice of the animals by exsanguination, after sacrifice in deep nembutal anesthesia by exsanguination, and after 24 hours of fasting and then sacrifice in deep nembutal anesthesia by exsanguination.

Several points concerning the relative fat globule counts are worthy of note. First the fat globule counts in the same tissues of different animals in each group were of the same order of magnitude. Second, a fairly consistent fat count ratio of about 10 to 1 was maintained between gray and white brain matter.

Probably sacrifice by exsanguination reveals more nearly the picture which is present in the living animal. When instead the animal was deeply anesthetized by nembutal for 10 to 15 minutes before sacrifice by exsanguination, a very different picture was seen. The counts in the lungs and brain increased, but in particular the counts in the brain increased. The mechanism of this change will be discussed later. On the other hand a 24 hour fast prior to sacrifice by exsanguination during deep nembutal anesthesia lowered the fat globule counts to the levels seen when sacrificed by exsanguination without anesthesia. It is clear that absolute control studies cannot be had for the type of study to follow since in every instance shock, nembutal anesthesia, and fasting complicated the experimental conditions which we produced.

Effects of fracture of the femur and of muscle contusion on the fat globule counts in the lungs and brain. For this study the femurs of lean animals were fractured under light nembutal anesthesia and the animals were subsequently sacrificed by overwhelming doses of nembutal at intervals of 3, 6, 12, 24, and 48 hours. In each instance a series of parallel control studies was run in which the muscles of the thigh on one side were severely contused. These animals were killed by the same means and after the same lapses of time. For each time interval 3 animals were used. The fat globule counts in the lungs and in both the gray and white matter of the brains are listed in Table II, but in Figure 20 only the counts for the lungs and total counts for the brain (gray plus white matter) are plotted.

After severe muscle contusion alone significant variation of the fat globule counts were not noted in the lungs and different parts of

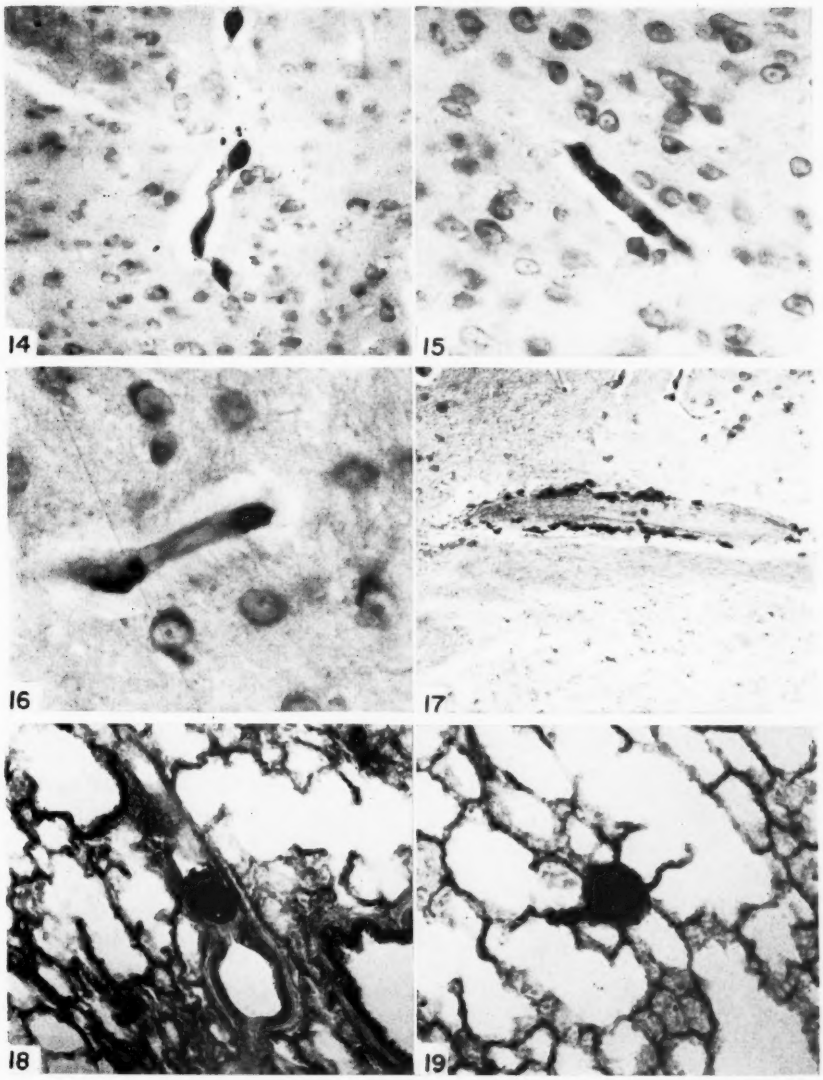

Fig. 14. Experimental studies of rabbits. Two fat emboli in one blood vessel of the rabbit's cerebral gray matter. Staining as in Figure 7, ×239.

Fig. 15. Large fat globules in blood vessel of rabbit's cerebral gray matter. Staining as in Figure 7, ×266.

Fig. 16. Emboli in small blood vessel of rabbit's cerebral gray matter. Staining as in Figure 7, ×429.

Fig. 17. Moderately large blood vessel in brain containing much fat in its wall. Staining as in Figure 7, ×99.

Fig. 18. A large fat embolus in a pulmonary artery. Staining as in Figure 7, ×99.

Fig. 19. A fat embolus in a pulmonary vessel. Staining as in Figure 7, ×120.

TABLE II.—EFFECTS OF FRACTURE AND MUSCLE CONTUSION ON FAT GLOBULE COUNTS

Time intervals, hr.	No.	Lungs	Aver.	Brain: Gray matter	Aver.	Brain: White matter	Aver.	Brain: Total	Aver.
	Fractures								
3	25	75	100	50	65	23	13	82	78
	26	100		51		11		62	
	27	125		86		6		92	
6	12	45	81	94	70	19	18	113	88
	13	95		70		18		88	
	14	105		46		16		62	
12	15	70	85	14	43	3	5	17	48
	16	80		51		5		56	
	17	105		63		6		69	
24	18	80	273	30	43	6	5	36	48
	19	390		43		4		47	
	20	350		57		5		62	
48	21	240	256	78	48	15	12	93	60
	22	315		56		19		75	
	23	215		11		3		14	
	Muscle contusions								
3	34	15	25	46	47	8	13	54	60
	35	20		32		12		44	
	36	40		62		19		81	
6	37	60	38	46	38	3	4	49	42
	38	35		31		4		35	
	39	20		37		4		41	
12	41	0	25	38	47	9	7	47	54
	42	55		57		5		62	
	43	20		114*		12*			
24	28	25	28	38	43	6	9	44	52
	29	35		42		12		54	
	30	25		48		8		56	
48	31	5	10	60	57	8	8	68	65
	32	10		56		8		64	
	33	15		56		8		64	

*These 2 results were not used in obtaining the averages, as the figure for the gray matter was "out of line" with the other values.

the brain (Table II; Fig. 20). However, when one femur was fractured two changes were evident. First, 3 and 6 hours after the fracture the counts in the brain (both gray and white matter) were elevated. The counts in the brain then dropped to a level comparable to those seen after muscle contusion. Second, the number of fat globules in the lungs increased significantly 24 and 48 hours after the fracture. It should be noted that for at least the first 24 hours after fracture or after muscle contusion the rabbits ate very little food, and therefore should be considered as fasting. This fact is of importance in the interpretation of this and subsequent data.

Effect of fattening and of fasting on the fat globule counts after fracture. From Table III it would appear that in fat animals the fat globule counts in the lungs 24 hours after fracture were significantly higher than in lean animals. A 48 hour fast prior to sacrifice appeared to lessen the fat globule counts in the lungs of fat animals 24 hours after fracture. Note also in Table III that the fat counts in the brain did not change as did the counts in the lungs. In other studies, not listed in the tables, large fat meals were given to rabbits 3 to 6 hours prior to sacrifice. These meals neither caused a significant lipemia nor altered the fat globule counts in the lungs or brain.

DISCUSSION

The method of visualizing the fat in the lungs and brain was satisfactory. The black staining neutral fat could be clearly identified in the alveoli and blood vessels of the lung and in the blood vessels, vessel walls, and perivascular spaces of the brain. Very little of the fat in the brain was in macrophages, but much of it was present as droplets 3 to 8 micra in diameter in the vessel walls and perivascular spaces. Our method of estimating the relative amounts of fat is semiquantitative at best. Fortunately the changes which occurred in the fat counts were great enough to allow us to draw some tentative conclusions from these methods. It is obvious that much more fat was present in the lungs at all times than in like areas of brain. The total counts per unit of area in the gray matter of the brain and lung were about the same, but the fat droplets in the lungs were much larger than in the brain. The white matter of the brain contained much less fat than the gray matter, a reflection in all probability of the relative abundance of blood vessels in the gray matter.

The source of intravascular fat emboli is incompletely known. After fractures of large bones, it seems clear that bone marrow fat contributes to these emboli, but many writers have expressed doubt that there is enough fat in the bones to cause, by itself, clinical signs of embolism. This point of view is strengthened by the experiments of Lehman and Moore which indicated that a very large amount of cottonseed oil can be injected into the blood stream of experimental animals before symptoms of embolism develop. Other

similar observations in humans have supported this view. Recent observations suggest, however, that the tolerance of human beings for injected fat may be much lower than was previously thought, and much lower than is the tolerance of experimental animals. However, there is the observation that clinical fat embolism may occur after injuries in which there is no fracture, or even in the absence of physical trauma, i.e. in patients with diabetes mellitus, and following simulated high altitude flights.

It has been suggested that the blood fat is in suspension as chylomicra clusters or coalesces to form embolic droplets of fat, or that the dissolved fat comes out of solution and forms emboli when the bone fat is added to the blood. Presumably a supersaturated state of the dissolved blood lipid results from the addition of the marrow fat to the blood and a lipemia too heavy to remain stable develops. Still others have suggested that "tissue juices" liberated into the blood as the result of fracture and the resultant tissue injury cause the dissolved fat to come out of solution. This latter concept was not supported by our own studies, since massive and severe contusion of the thigh muscles was not followed by an increase in the circulating free fat globules.

Finally, the alimentary lipemia has been considered a source of fat emboli. Weld demonstrated that following heavy fat meals the fat in the lungs increased in dogs and cats. In our rabbits an increase of the lung or cerebral fat did not occur after single large fat meals in 6 animals. However, heavy feeding for several weeks was followed by an increase in the lung fat following fracture and fasting decreased the amount of fat in the lungs. That the state of nutrition may be a factor in the frequency and severity of fat embolism in humans is indicated by the study of Zeithofer and Reiffenstuhl. These workers reported that prior to World War II the frequency of fat embolism in routine postmortem studies in Vienna was 4.7 per cent, whereas during the war the incidence of fat embolism was 0.4 per cent. This decrease was related to the reduced caloric intake of the general population due primarily to a lessened fat intake.

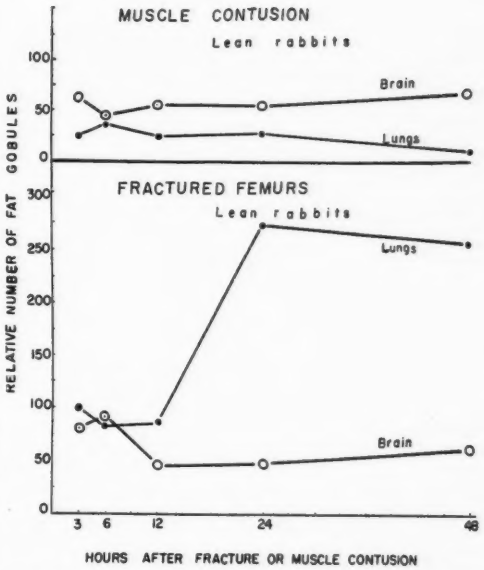

Fig. 20. Schematically shows the changes in the relative fat content of the brain and lung at variable periods after either muscle contusion alone or fracture of one femur.

Our studies of "normal control" material (Table I) indicate that freely circulating fat globules are present in the vascular system under "normal" circumstances, and that these fat globules may be a heavy contributor to fat embolism. The amount of this fat is apparently reduced by fasting, and increases during a period of weight gain due to increased food intake. This circulating fat probably accumulates slowly by the aggregation of chylomicra into clumps which later form globules. Droplets of fat are to be seen frequently floating on top of whole blood samples immediately after withdrawal from dogs with heavy alimentary lipemias. It is to be noted that in clinical Case 1 of this paper free fat droplets were observed in the blood.

The circulating fat globules probably pass slowly through the capillary beds of the body and under usual circumstances most of them are held in the capillary beds of the general circulation. The lungs function as a filter in the vascular system and normally prevent "showers" of fat to the brain and to the rest of the body. In the normal process of filtering

TABLE III.—EFFECT OF FATTENING ON FAT GLOBULE COUNTS AFTER FRACTURE

Treatment	No.	Globule counts after fracture							
		Lungs		Brain					
			Aver.	Gray matter	Aver.	White matter	Aver.	Total	Aver.
Lean rabbits	18	80	273	30	43	6	5	36	48
24 hours fracture	19	390		43		4		47	
	20	350		57		5		62	
Fat rabbits	82	1115	831	63	41	7	3	70	44
24 hours fracture	83	1020		29		1		30	
	84	360		30		1		31	
Fat rabbits	88	495	543	37	25	1	2	38	27
24 hours fracture	89	350		13		3		16	
48 hours fasting	3	785							

these circulating fat globules from the blood, the fat content of the lungs varies considerably, whereas the fat content of the brain varies little (Table III).

Under circumstances which reduce the vascular tone, such as nembutal anesthesia or shock due to fracture of the femur, the globules of fat held in the general circulation are probably washed out of the vascular bed, and to the lungs. These fat droplets quickly pass through the relaxed vascular bed of the lungs and find their way to the brain and general circulation again. If the quantity of this circulating fat is great enough, and the pulmonary blood vessels are sufficiently relaxed, the amount of fat in the cerebral circulation at any one time may become sufficient to cause serious tissue ischemia and pathologic changes. Studies of the cerebral circulation (9) have shown that very large numbers of paraffin emboli must be injected simultaneously into the carotid artery to produce lesions in the brain. In this study it was also shown that anesthesia by nembutal greatly facilitates the passage of the emboli through the brain. The relaxing effect of anesthesia (and presumably of shock) on the vascular system of the brain is probably more than balanced after large bone fractures or anesthesia by the increased number of circulating fat globules released from the relaxed vascular bed of the general circulation, and by failure of the lungs to filter the excess of this fat from the blood. It is also possible that due to the constricting dural envelope of the brain the cerebrovascular system is unable to dilate as effectively as the vascular system of the lungs and of the general circulation. If this is true, then the cerebrovascular system during shock may become a more efficient filter for circulating fat globules in the blood stream than the vascular bed of the rest of the circulatory system.

In addition to the effect which circulating fat produces by itself, it is necessary to consider the recently demonstrated factor of aggregation and adhesiveness of the red blood cells which follows large fat meals (6, 7). These adhesive and aggregated red blood cells might well contribute to the problem by forming emboli by themselves or by adhering to the fat globules much as did fibrin in the cases reported by Cammermeyer.

It is of interest that most of the fat which collected in the brain was in the vessel walls or extravascular spaces. This would seem to indicate that the neutral fat globules pass through the endothelial linings of the cerebral blood vessels very rapidly. If each large fat globule outside a blood vessel was previously a fat embolus, then a large percentage of vessels were at one time temporarily occluded in some of our rabbits and also in the clinical cases of fat embolism. In the rabbits it can be said with reasonable certainty that this extraluminal fat had its origin from the blood stream as control animals demonstrated very little of this fat, and it seems unlikely that the fat could have arisen from the brain tissues in so short a time (15 minutes).

Following fracture the fat content in the blood probably starts to increase immediately due to addition to it of bone marrow fat. The excess of this fat is probably held as globules in the lungs and in the capillary bed of the general circulation where it becomes a part of the freely circulating fat. If the circulating visible fat is not too great in amount the excess of it is slowly removed from the circulation and no untoward symptoms develop. If it is excessive in amount, symptoms of pulmonary embolization occur after 1 or 2 days. If the lungs are unable to retain the fat, "showers" of fat go to the brain. Signs of cerebral damage then develop. Our clinical observations and experimental studies also indicate that cerebral embolization may occur

immediately after fracture. It is our belief that this occurs during anesthesia or when shock is present. Either of these factors could relax the vascular bed so that the circulating globules held in the capillary bed of the general circulation could pass through the lungs to the cerebral circulation. The possibility that this occurs in humans is supported by our own personal observations of patients and by reported cases referred to before. In those cases in which cerebral embolization occurs early pulmonary symptoms have not been prominent, presumably because fat is not blocking the circulation of the lungs.

If the concept introduced in the paper is correct, that a variable amount of fat circulates constantly as fat globules, it is possible to explain the origin of fat embolism in non-traumatic cases such as in patients with diabetes mellitus and in others after simulated high altitude flights. It would also help to explain why the state of nutrition is an important factor in determining the frequency of fat embolism.

The diagnosis of pulmonary or cerebral fat embolism is usually made in retrospect and can only be suspected early in its clinical course. Yet it should be possible to anticipate the syndrome. One would expect the visible fat (fat visible in dark field illumination as chylomicra or in plasma as a visible turbidity) to increase sharply before clinical symptoms develop. If this occurs after fracture and during a period of fasting, or if large fat droplets appear in the blood, one should anticipate the possible development of clinical signs of fat embolism. Alimentary lipemias usually reach their peak in 2 to 4 hours and then clear by the end of 6 to 9 hours. If one observes a lipemia after fracture which continues to rise instead of fall 4 hours or longer after eating, one would suspect an abnormal accumulation of fat in the blood stream. If symptoms of pulmonary embolization should occur with a clear or clearing plasma one would suspect that the emboli were not fat globules but aggregates of adhesive red blood cells or other particulate material.

To treat fat embolism effectively, one must anticipate its occurrence and take steps to prevent its development. It is important to keep in mind the source of the emboli. Fractured bones should be effectively and quickly immobilized to minimize the amount of fat supplied to the blood from the broken bone. It is probably of equal importance to prevent shock and avoid anesthesia since these measures allow the mobile fat globules in the vascular system to pass through the lungs (where they normally are held) to the brain. It is perhaps wise also to allow patients with fractured bones little food for 48 to 72 hours. This should be fat free. As yet no report of a trial of heparin for treatment of fat embolism has appeared. It is well known that injections of heparin can cause the turbidity in the blood due to an alimentary lipemia to disappear, and recent studies have shown that amounts of heparin too small to alter the clotting time can cause clearing of a lipemia. If it can be shown that heparin can cause the fat which is responsible for fat embolism to go into solution, then this drug may be of great usefulness in the treatment of fat embolism. It should be kept in mind, however, that if sufficient heparin is injected to increase the clotting time of the blood then cerebral hemorrhage becomes a real danger. Furthermore, heparin is a potent biologic substance with varied functions. One would be wise to treat it with circumspection.

SUMMARY

The early onset of cerebral fat embolism without pulmonary signs and symptoms has been emphasized, and 2 cases of cerebral fat embolism demonstrating these features have been described.

The mechanism of cerebral fat embolism and, in particular, early cerebral fat embolism has been studied experimentally in rabbits. These studies suggest that an important source of the fat emboli is circulating fat globules which are held much of the time in the capillaries of the general and pulmonary circulation. The circulating fat probably has its origin from the chylomicra, and it is increased by heavy feeding for several weeks and decreased by fasting.

The early onset of cerebral symptoms of fat embolism is due probably to either shock and unconsciousness or to anesthesia, all of which

presumably relax the vascular bed and allow the circulating fat plus the fat from the fractured bones to be washed through the pulmonary circulation to the brain.

It is suggested that dark field examination of whole blood to determine the amount and sizes of the circulating fat globules in the blood would be a useful adjunct to the early diagnosis of fat embolism.

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MANAGEMENT OF THE SURGICALLY INJURED URETER

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THE steadily increasing number of radical gynecologic and general surgical procedures performed in the pelvis has resulted in an ever-increasing number of cases of ureteral injury. According to Ingersoll and Meigs "Accidental injury to the ureter is the most frequent serious complication of gynecological pelvic surgery." Because of the close relationship of the lower ureter to the important pelvic structures, most injuries take place in the lower third of the ureter, and, therefore, this report will be limited to a discussion of injuries of only that portion of the ureter. Twenty cases of low ureteral injury seen by the Urological Service of the Rhode Island Hospital during the past 5 years have been studied and form the basis for this investigation and report.

Although in each instance of injury to the ureter the treatment must be individualized, there are several principles which serve as useful guides not only for treatment but also for prevention.

1. Most urologists agree that a more frequent use of preoperative catheterization of the ureters would go far to reduce the number of ureteral injuries, but for an as yet unexplained reason most gynecologists and general surgeons are reluctant to adopt this simple safeguard. Admitting, therefore, that it is either very difficult or impossible to popularize this procedure, we still suggest that preoperative intravenous urograms at least should be performed on all patients about to undergo major pelvic surgery. Not only does this afford an estimate of the renal function and anatomy on each side, but it also gives warning of any involvement of the ureters in the pelvic disease. Such preoperative knowledge should considerably lessen the incidence of ureteral injury, and in addition would place the surgeon in a much more advantageous position should such injury accidentally occur. There is the further advantage that pre-existing renal and ureteral abnormalities will be discovered, and in the event of postoperative urinary complications these will not be blamed on the surgeon.

2. Recognition of ureteral injuries at the time of the initial surgery is of the greatest importance. Some type of immediate repair can always be effected and thus prevent the troublesome complications of extravasation, fistula, or renal damage. Furthermore, the patient often recovers without added length of hospitalization.

3. Finally, preservation of renal function is naturally of paramount importance, and every effort should be made to solve the problem without resorting to nephrectomy. This is a frequently repeated statement but unfortunately a large number of nephrectomies are still being done. The previous expedient of ureteral ligation can be more often supplemented by ureteral anastomosis or reimplantation to the bladder.

Accidental injuries to the ureter may for the purposes of this discussion be divided into two groups—those injuries recognized at the time of the operation and those recognized in the postoperative period. The ureter may be ligated, angulated by a suture, included in a suture, crushed, cut (with or without complete severance), or a portion may be resected.

IMMEDIATE TREATMENT OF URETER INJURED AT OPERATION

Although generally not recognized at the time of operation, the ligated ureter is the simplest form of ureteral injury to deal with. Most operators agree that removal of the suture and retrograde ureteral catheterization with a plastic catheter are all that is required. Periodic follow-up and dilatation in the event of stricture formation would of course be necessary. An angulated ureter and an incised ureter may be treated in a similar fashion except that in the latter it is important that

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Fig. 1. L.P. Left ureterovesical implantation, 2 weeks postoperative. Intravenous urogram (30 min.). Note mild left hydronephrosis.

Fig. 3. M.N. Right ureterovesical implantation, 12 weeks postoperative. Intravenous urogram (15 min.). Note normal right pyelogram.

Fig. 2. L.P. Left ureterovesical implantation, 12 weeks postoperative. Intravenous urogram (15 min.). Note normal left pyelogram.

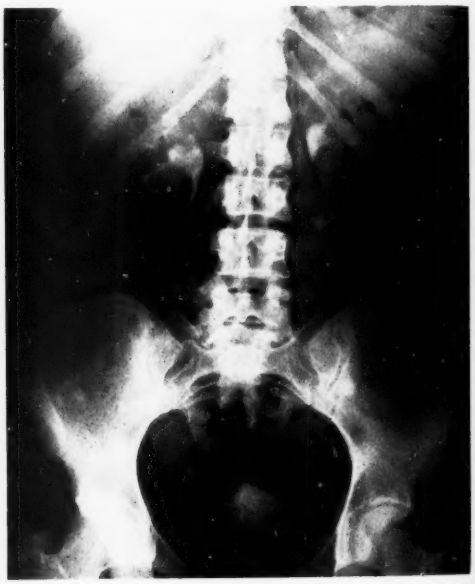


Fig. 4. W.E. Left ureterovesical implantation, 1 year postoperative. Intravenous urogram (15 min.). Note normal left pyelogram.

the area of incision be drained extraperitoneally.

Crushing the ureter with a clamp or severing it are more serious accidents. In the case of the crushed ureter it is generally believed that excision of the crushed portion must be carried out or severe stricture formation will result. Thus, crushing injury is no different from complete severance of the ureter. End-to-end anastomosis or implantation of the proximal end into the bladder are the two choices in this situation. The advantage of the former is the preservation of an intact ureterovesical junction, but serious disadvantages are the unfamiliarity of most surgeons with this procedure and the high incidence of postoperative stricture even with the most experienced management. On the other hand, ureterovesical implantation is relatively easy to perform, is not prone to stricture formation, but has the disadvantage of an artificial ureterovesical junction and the attendant danger of reflux. Relying on our successful experience with ureterovesical implantation in other situations, we have favored this type of repair. The method used is described by Stevens and Marshall and consists of implanting the split ureter through a stab wound, made in an oblique direction as low in the bladder as possible, in order to imitate the usual course of the intramural ureter. This is best done through the open bladder to facilitate intravesical manipulation. The ureter, which should protrude into the bladder about ½ centimeter without tension, is anchored by suturing the two flaps to the bladder mucosa within the bladder and also by suturing the adventitia of the ureter to the posterior bladder wall. A plastic splint may be used for 48 to 72 hours and brought out through the opening in the bladder; the extravesical area at the site of the anastomosis should be drained extraperitoneally. The bladder is sutured around a small mushroom catheter which is placed on constant drainage.

Resection of a portion of the ureter in such a way that neither anastomosis nor bladder implantation is possible is the most serious situation one has to deal with, and one which too often in the past has been handled by purposely ligating the ureter or by nephrectomy. It is our opinion that when this accident occurs in the lower third of the ureter a plastic bladder flap can be successfully utilized to bridge the gap and thus save the kidney. This method will be fully described later.

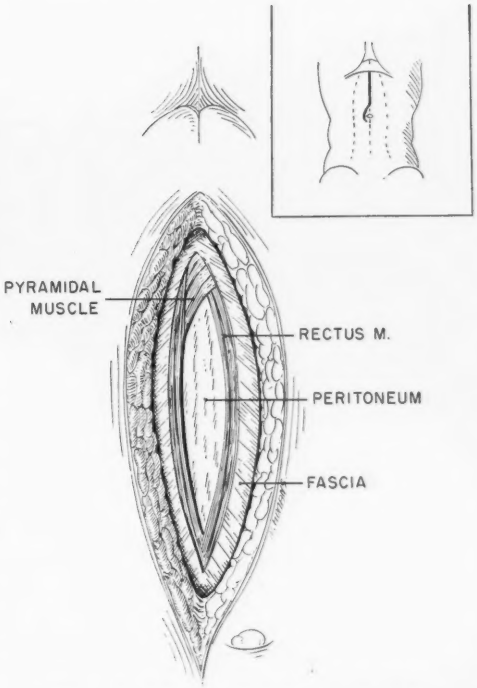


Fig. 5. A midline suprapubic incision is made.

Among the cases we have chosen for study, there were 9 in which accidental injury to the ureter occurred and was recognized at the time of operation. Only 2 of these cases were treated in conjunction with the urologic service at the time of the operation. Both of these were cases of unilateral ureteral severance and both were treated by implantation of the proximal ureter into the bladder. The postoperative results in these were good, as judged by intravenous urograms 2 and 12 weeks after operation (Figs. 1, 2, and 3).

In the remaining 7 cases there were 2 patients with unilateral ureteral severance treated by bladder reimplantation who apparently did well clinically. In a third case the ureter was purposely ligated after being cut and this

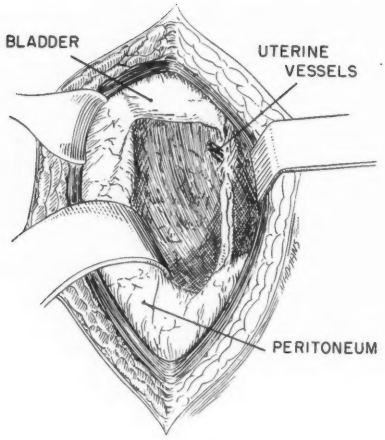
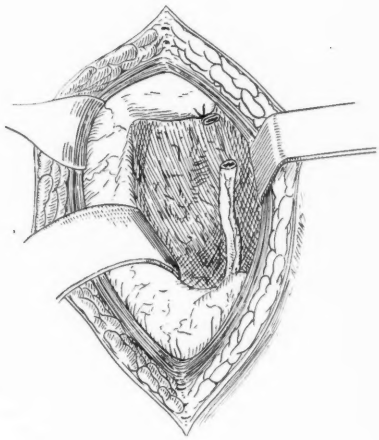


Fig. 6.



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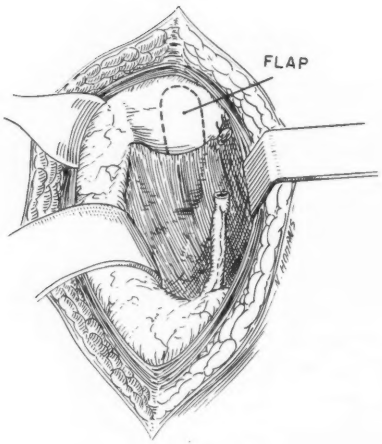


Fig. 8.

Fig. 6. The ureter is exposed extraperitoneally and can be seen involved in cicatrix near its lower end.
Fig. 7. The scarred area is excised and the distal stump ligated.
Fig. 8. The bladder flap is outlined.

patient recovered uneventfully. In a fourth case the ureter was cut 8 to 10 centimeters above the bladder and an end-to-end anastomosis was attempted over a No. 6 ureteral catheter, but the site of anastomosis was not drained postoperatively. The patient developed a ureterovaginal fistula 23 days after operation and was found to have a ureteral stricture and a pyohydronephrosis in a nonfunctioning kidney. She fortunately had a normal kidney on the other side, so that nephrectomy could be performed. She then made an uneventful recovery. In a fifth case the ureter was incompletely severed. Treatment consisted of repair around a ureteral catheter, but again the area was not drained. She developed a pelvic abscess drained by colpotomy 7 days after operation, after which a ureterovaginal fistula formed which lasted 8 weeks and then healed spontaneously. She had a normal pyelogram after this and has remained well. In a sixth patient with a similar injury repair was carried out with drainage and the patient made an uneventful recovery.

The seventh patient suffered complete severance of both ureters during a difficult hys-

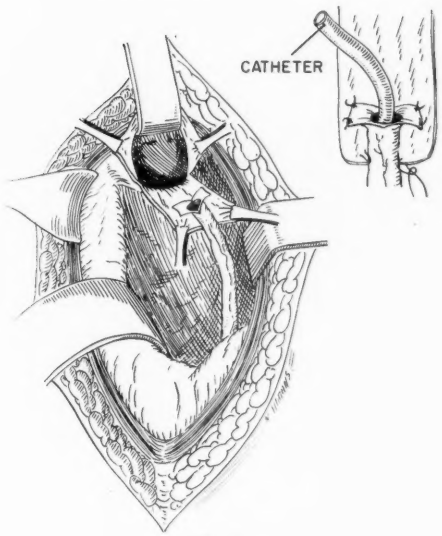
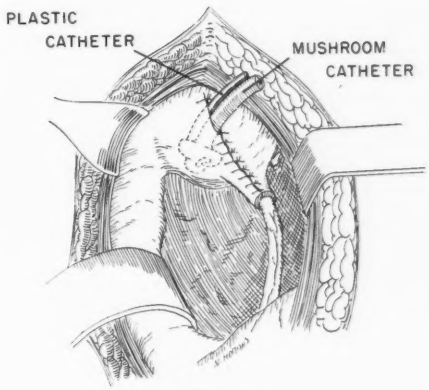


Fig. 9.



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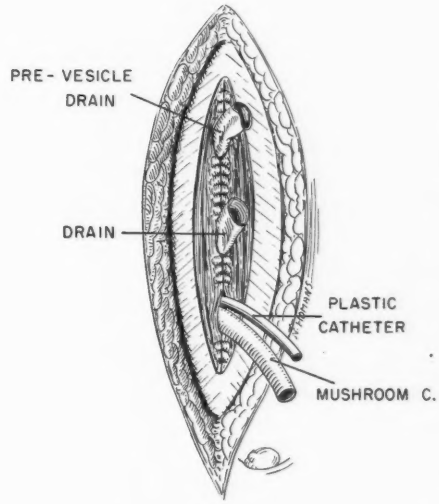

Fig. 11.

Fig. 9. The bladder is opened and the flap brought up to meet the cut end of the ureter. Anastomosis is made around a plastic ureteral catheter.
Fig. 10. The flap is rolled upon itself and the entire bladder is closed.
Fig. 11. Wound closure.

terectomy and was treated by bilateral ureterovesical implantation from behind, without opening the bladder and without draining the sites of implantation. On the left side, the implantation was successful, but the patient developed a right ureterovaginal fistula. Her subsequent treatment will be described later.

DELAYED TREATMENT OF URETER INJURED AT OPERATION

Ureteral injuries not recognized until the postoperative period tend to be regarded as more definitely in the urologist's realm, and it is in these difficult situations that he is most often consulted. In a general way complications of this type are limited to the effects of ureteral obstruction, or the leakage of urine from the injured ureter causing either extravasation of urine alone, or a ureterovaginal or abdominal fistula or both.

Unilateral ureteral ligation often goes unnoticed, particularly if there is no pre-existing renal infection and the other kidney is normal. On the other hand, incomplete obstruction of

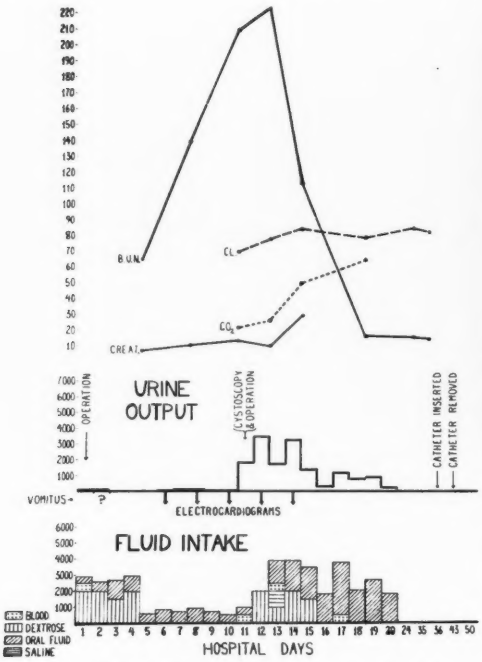

Fig. 12. E.M.S. Hospital course including blood chemistries and fluid treatment.

Fig. 13. E.M.S. Left ureterovesical anastomosis using bladder flap method, 12 weeks postoperative. Intravenous urogram (15 min.). Note mild left hydronephrosis and hydroureter with prompt excretion of diodrast. There is no excretion from the left kidney.

one ureter, caused by a partially tied suture or by angulation, will usually become apparent by the development of renal infection or pain and can be evaluated by intravenous urogram. A preoperative urogram will be very useful for comparison here.

In our series there were 11 cases of injury to one or both ureters not recognized at the time of operation. Two of these resulted in incomplete unilateral ureteral obstruction. One was treated by ureterolysis, and the second, in whom the injury occurred in the intramural portion, required a plastic meatotomy through the open bladder. Both of these patients recovered, have normal pyelograms, and are well to date.

Bilateral ureteral ligation causes complete anuria and can easily be recognized if the urinary output is observed. One cannot emphasize too strongly that anuria following major pelvic surgery demands early cystoscopic investigation to rule out bilateral ureteral obstruction. Two cases of bilateral ureteral ligation occurred following panhysterectomy. The first was treated by an attempted deligation on the day after operation, but the anuria persisted and at reoperation a bilateral ureterovesical implantation was successfully carried out. This case serves to illustrate the difficulties of emergency ureteral deligation and suggests that nephrostomy followed at a later time by a plastic procedure to the ureter is the method of choice. This plan was carried out in the second case of bilateral ureteral ligation, with good success.

The remaining 7 cases of ureteral injury all are instances of urinary extravasation in the form of a pelvic abscess, usually associated with a ureterovaginal or abdominal fistula.

Two of these patients were treated by nephrectomy, largely because the severity of the local infection contraindicated any attempts at repair. Two other patients with a persistent ureterovaginal fistula were treated by

ureterovesical implantation with good results in each (Fig. 4). In the last 3 cases there were 2 ureteroabdominal fistulas and 1 ureterovaginal fistula; in each case the injury occurred high enough so that ordinary ureterovesical implantation was not possible. In each of these cases it was possible to perform a ureterovesical anastomosis by constructing a bladder flap and utilizing this to bridge the gap.

The procedure, based on an operation which was originally done experimentally on dogs by Boari, and reported in 1894, is simple and can be applied both to injuries discovered at the time of operation and to injuries discovered later. It has been previously described by several authors, among them Ockerblad, Hicks, Henderson, and Caughlan, each of whom have reported a successful case.

The ureter is exposed extraperitoneally in the usual fashion, although a midline incision is preferable since it affords greater ease in handling the bladder (Fig. 5). The lower end of the ureter is freed and the scarred portion excised (Figs. 6 and 7). If one finds at this time that there is not enough length to permit the usual type of ureterovesical implantation without tension, the bladder is opened in the midline and a flap of sufficient length is taken to bridge the distance and allow the ureter to overlap it for about 1 centimeter without tension. The ureter is bivalved and the flaps are sutured to the bladder mucosa. In addition, the adventitia of the ureter is sutured to the bladder wall with several fine absorbable sutures (Figs. 8 and 9). The bladder flap is then rolled upon itself to form a tube and sutured around a suprapubic catheter. A plastic catheter also brought out suprapubically is used as a splint and as a drain for the renal pelvis (Fig. 10). The wound is closed in the usual manner and two small drains are left in the prevesical space and at the site of anastomosis (Fig. 11).

This operation has been performed in 3 cases with entirely satisfactory results. (Two additional patients were operated upon in November of 1953 and have been well up to the present time.)

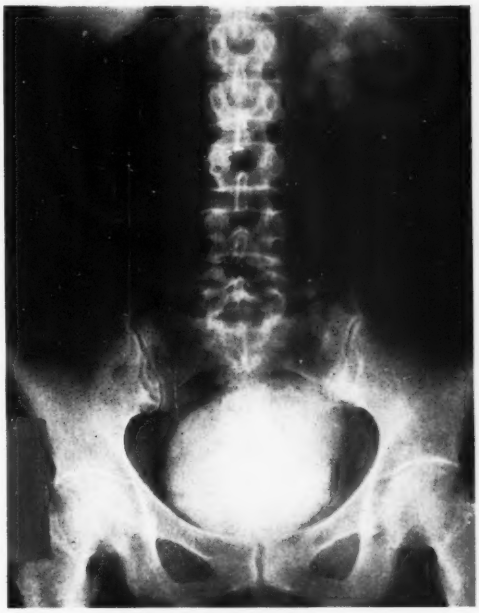

Fig. 14. E.M.S. Same intravenous urogram (75 min.). Note appearance of bladder flap and site of anastomosis.

CASE 1. E.M.S., a 62 year old single female, was admitted to the hospital as an emergency because of sudden severe lower abdominal pain and was subjected to a total hysterectomy for a ruptured papillary cystadenocarcinoma of the ovary. Her general condition as well as the amount of blood lost during the operation necessitated the administration of several blood transfusions. Following operation, she was anuric and remained so until the eighth postoperative day when she was first seen in consultation by the urologic service. Her output on that day was 90 cubic centimeters and it was thought that she was probably recovering from lower nephron nephrosis. Cystoscopic examination was, therefore, deferred. However, by the tenth day her output had not increased, and cystoscopic examination was carried out. This revealed an obstruction in the left ureter about 5 centimeters above the bladder and a relatively nonfunctioning aplastic right kidney. Immediate deligation and insertion of a T tube into the left ureter at the affected site were carried out. The patient made a good postoperative recovery, and her blood urea nitrogen, which was 220 prior to operation, became normal in 8 days. She was discharged from the hospital 3 weeks after removal of the T tube, voiding normally and with a well healed wound (Fig. 12). Three weeks after discharge, urine began to drain through her abdominal wound and she stopped voiding. Cystoscopic examination revealed an impassible ureteral stricture about 5 centimeters above the bladder. In November, 1950, twelve weeks after

Fig. 15. E.S. Right ureterovesical anastomosis by bladder flap method, 12 weeks postoperative. Intravenous urogram (5 min.). Note prompt excretion of diodrast on right.

Fig. 16. E.S. Same intravenous urogram (45 min.). Note normal right pyelogram, with bladder flap well outlined and normal caliber of right ureter.

the original operation, her left ureter was explored. A densely scarred area was found about 5 centimeters above the bladder, and when the ureter had been freed upward to where it became normal, there was insufficient length to carry out a ureterovesical implantation. Accordingly, a plastic ureterovesical anastomosis using a bladder flap was carried out. The patient recovered slowly and was discharged on the twenty-fourth hospital day with a dry wound and a blood urea nitrogen of 10 milligrams per cent. At the present time, 3 years later, she is free of urinary symptoms, has a normal urine and blood urea nitrogen, and works regularly at her job. Intravenous urograms carried out 12 weeks postoperatively (Figs. 13 and 14) show a mild left hydronephrosis and hydroureter. These have been repeated at yearly intervals (1952 and 1953) and there is absolutely no change. The patient has remained well to date.

CASE 2. E.S., a 44 year old single female, was first operated on in July of 1951, when a total hysterectomy for chronic inflammation of the tubes and ovaries was carried out. During the operation, both ureters were completely severed near the bladder. A bilateral ureterovesical implantation was carried out at the time of operation from behind, but without extraperitoneal drainage. Although the left ureterovesical implantation was successful, she developed a ureterovaginal fistula on the right side. This continued for 5 months, and she was readmitted to the hospital in December of 1951, at which time her right ureter was explored. As in the previous case, when the ureter had been mobilized and freed from scar tissue it was found to be too short to permit a ureterovesical implantation. A ureterovesical anastomosis using the bladder flap method was therefore performed. The patient made a normal postoperative recovery and was discharged on the eighteenth postoperative day with a dry wound, voiding normally and with no vaginal leakage. She has remained entirely free of urinary symptoms, has a normal sterile urine and blood urea nitrogen, and is able to work at her usual occupation. Intravenous urograms carried out 12 weeks postoperatively (Figs. 15 and 16) show no hydronephrosis or hydroureter on the right. These studies were repeated in 1952 and 1953 and showed no change. The patient has remained well to date.

CASE 3. M.R., a 45 year old female patient, was admitted to the hospital because of vaginal bleeding, and 5 days later had a radical hysterectomy with pelvic lymphadenectomy for a leiomyosarcoma of the uterus. Postoperatively, a left ureteroabdominal fistula developed. Approximately 2 months after her original operation the left ureter was explored and found to be involved in dense scar tissue at a distance of about 6 centimeters from the bladder. After being freed, it was too short to permit a ureterovesical implantation and, therefore, a ureterovesical anastomosis using a bladder flap was carried

out in April 1952. The patient's postoperative course was complicated by wound infection and an atonic bladder, but she was finally discharged 6 weeks postoperatively voiding fairly well but with a residual of 4 to 6 ounces and with slight suprapubic drainage. This situation gradually improved over a period of 2 to 3 months. At the present time, 1 year since her original operation, her wound is dry, she voids with only about 1 ounce of residual, and her general condition is good.

SUMMARY

1. Ureteral injuries are becoming more frequent because of an increasing number of pelvic operations.

2. Preoperative roentgenograms of the urinary tract are advisable to study its anatomy and to evaluate the degree of involvement of the ureters in the pelvic disease.

3. Ureteral injuries, if they occur, are best corrected at the time of the original injury; and the site of ureteral incision, repair, anastomosis, or implantation should always be drained extraperitoneally.

4. Ureteral injuries in the lower third of the ureter can usually be corrected without resorting to ureterosigmoidostomy, ureterocutaneous anastomosis, or nephrectomy. If the remaining ureter is of sufficient length, a ureterovesical implantation can easily be done, and a successful postoperative result may be expected.

5. If there is insufficient length to carry out a ureterovesical implantation, a plastic ureterovesical anastomosis using a bladder flap can be carried out either at the time of the injury or at a subsequent operation. Our experience with 3 such cases is reported and has been very satisfactory.

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AN ELECTROMYOGRAPHIC STUDY OF CERTAIN MUSCLES OF THE LEG AND FOOT IN THE STANDING POSITION

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THE primary aim of this study was to determine the types of electromyographic activity found in three muscles of the leg and three intrinsic muscles of the foot. The muscles of the leg were tibialis anterior, peroneus longus, and the lateral head of gastrocnemius; the intrinsic muscles of the foot were abductor hallucis, flexor digitorum brevis, and abductor digiti minimi.

Most of the subjects were tested in different postures and during a variety of movements. Often, other muscles were examined as well. The present report concerns only the findings in the muscles named during the "relaxed standing at ease" position. In this regard we were especially interested in testing the validity of the popular theory that peroneus longus, tibialis anterior, and the intrinsic muscles of the foot maintain the arches of the foot in ordinary standing.

Special attention was also paid to the possible influence of certain variable factors, such as the sex of the subject, the type of feet, and the wearing of high heels by women.

MATERIAL AND METHODS

The subjects were chosen at random and were all relatively healthy young men and women volunteers. For the studies of the muscles of the leg there were 17 men and 16 women from whom the results were complete enough to be included here. In all but 2 of these subjects all three muscles were tested. For the intrinsic muscles of the foot there were 14 subjects (12 men and 2 women), but several were not studied completely.

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This work was supported in part by a Canadian Government Public Health Grant to the Hospital for Sick Children for research in poliomyelitis in the recovery stage.

The apparatus consisted of a Philips, mark iv, clinical electromyograph, a highly reliable single channel instrument capable of high gain amplification with minimal distortion. Jasper and Forde have already described the prototype of this apparatus. A "unipolar needle electrode" paired with a ring-shaped skin electrode 1.5 inches in diameter was used in the manner described by Jasper and Ballem of Montreal. Because preliminary studies showed that the lower amplifications that are used by many investigators are often deceptive, all our records were made with high gains (1 inch on the cathode ray tube being the equivalent of 100 microvolts).

While the subject was lying relaxed, the ring-shaped skin electrode (coated with electrode jelly) was strapped in place over the most prominent part of the muscle to be tested. The needle was thrust through the skin in the middle of the ring and into the belly of the muscle. The needle electrode is a fine darning needle insulated except at its tip. Anesthesia was not required and in most cases the subjects insisted that there was little if any discomfort. Once the needle was properly in place it caused pain only on extensive movements. An earthing electrode was strapped over the lower third of the medial surface of the tibia. All the obvious tests were made to insure that the needle was properly in place and that the apparatus was in working order.

For each muscle, records were made while the subject was reclining (as a control), immediately upon his assuming the standing barefooted posture and after 2 minutes of standing. Considerable testing showed that the initial activity invariably found on changing a position falls off rapidly to the resting level and that the 2 minute interval is adequate. Moreover, many of the subjects were

tested at longer intervals (up to 15 minutes) with no change in the results.

Our permanent records are all more than several seconds in duration, the average being about 4 or 5 seconds. To augment these records, we paid constant attention to the changes taking place on the cathode ray tube and in the loudspeaker, although the latter was usually turned off if the subject appeared to be influenced.

Our "relaxed standing at ease" posture is the comfortable well balanced stance with the feet several inches apart and bearing equal weight, and with the hands clasped loosely behind the back. The relative position of the feet would show minor individual variations. However, the slight changes that were necessary for some subjects to conform to the standard position made no difference in their comfort or in the findings. To test the muscles of the foot it was necessary to have the subject stand on a pair of raised blocks with a narrow interval between to accommodate the projecting electrode.

In all but 2 of the women additional similar records were made from the muscles of the leg while high heels were being worn. The heels were all 2½ inches high except in 1 case in which they were 3 inches.

Permanent electromyographic records were made on continuous-strip 35 millimeter photographic paper moving at constant speed (5.7 inches per second). All the records were made from muscles of the right side as a matter of convenience.

The results of physical examination and pertinent history were noted for each subject in the study.

In analyzing the records we could not divide them arbitrarily into two clear-cut groups of "activity present" and "activity absent," as others have done. It became necessary to recognize four types of record which we have designated for convenience as O, ±, +, and ++. The O type of tracing presents no disturbance of the baseline greater than 10 microvolts and is considered to indicate "inactivity." It is seen in all the muscles of the lower limb when the subject is reclining, and in many muscles when the subject is standing (Fig. 1a and b).

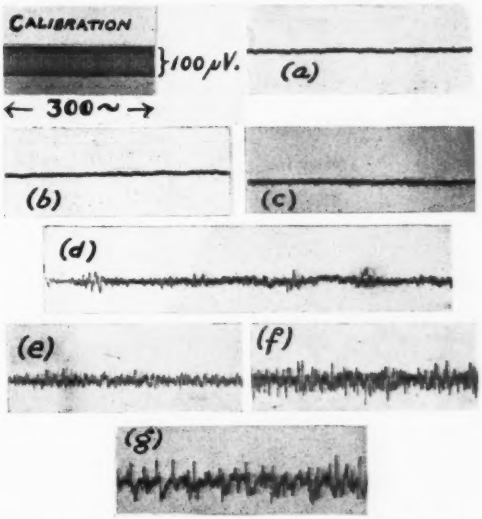

Fig. 1. Examples of different types of activity seen in tibialis anterior of different subjects while standing at ease and compared with record (a) made while a subject was reclining and completely relaxed. (b) o or inactivity; (c) ± or doubtful activity; (d) + or intermittent activity; (e), (f) and (g) ++ or continuous activity. These are short pieces taken from longer records.

The ± type of record includes those cases in which there are excursions of the baseline of 10 to 30 microvolts (Fig. 1c). These probably indicate activity in distant muscles but we did not wish to dismiss them or arbitrarily place them in the inactive group. Jasper and others have shown that, with unipolar needle electrodes, normal motor unit action potentials in the immediate neighborhood are well above 100 microvolts and usually about 1 millivolt. Our experience showed that many of the potentials over 30 microvolts were definitely from the muscle being tested.

The + type includes those tracings that show frequent, short, intermittent bursts of typical activity within the muscle being tested, with short, relatively quiescent intervals (Fig. 1d).

The ++ type includes those cases exhibiting the typical continuous "interference pattern" of normal activity. Although qualitative differences appear in the active tracings, no attempt has been made to differentiate them further (Fig. 1e, f, and g).

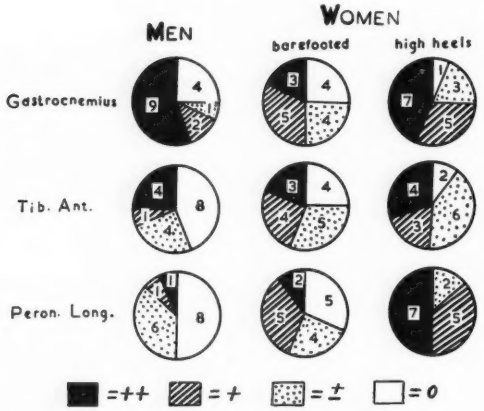

Fig. 2. Frequency of types of electromyographic activity in three muscles of the leg during relaxed standing at ease.

TABLE I.—FREQUENCY OF TYPES OF ELECTROMYOGRAPHIC ACTIVITY IN THREE MUSCLES OF THE LEG DURING RELAXED STANDING AT EASE

			Types of tracings, No.				
			++	+	±	o	Total
Gastrocnemius (lateral head)	Men		9	2	1	4	16
	Women	(barefooted	3	5	4	4	16
		(high heels	7	5	3	1	16
Tibialis anterior	Men		4	1	4	8	17
	Women	(barefooted	3	4	5	4	16
		(high heels	4	3	6	2	15
Peroneus longus	Men		1	1	6	8	16
	Women	(barefooted	2	5	4	5	16
		(high heels	7	5	2	0	14

RESULTS

Muscles of the leg. Table I summarizes the findings for the muscles of the leg in both males and females. These findings are demonstrated more clearly in Figure 2, which is a graphic representation of the table. Several important points emerge.

The lateral head of gastrocnemius was active in the majority of 32 subjects, no matter whether the ± group was included with the "actives" or with the "inactives." In the women, the ++ group is definitely smaller when the subjects were barefooted, but almost the same as in the males when high heels were worn. Four of 16 men and the same proportion of women showed no electromyographic activity in this muscle when the subject was barefooted. Analysis of individual cases revealed that only 1 of the 16 women continued to show no activity on wearing high heels.

Almost half of the men and a quarter of the women showed no electromyographic activity in tibialis anterior when barefooted. But 4 of 17 men and 3 of 16 women showed pronounced activity (which could be abolished by leaning forward). Individual analyses showed that all of the women in this latter group exhibited at least the same degree of activity on standing in high heels. One woman showed ++ activity in high heels but only ± activity while barefooted.

Only 1 of 16 men and 2 of 16 women showed ++ or continuous activity in peroneus longus. An additional man and 5 women showed + or intermittent activity. Half of the men and 5 of 16 women showed inactivity when barefooted. With high heels half of the women showed continuous marked activity and none showed inactivity in peroneus longus.

Intrinsic muscles of the foot. Table II and Figure 3 summarize the findings in the abductor hallucis, abductor digiti minimi, and flexor digitorum brevis.

Generally, there was very little activity in these muscles while standing. Nine of 12 abductors of the great toe, and 7 of 9 short flexors of the toes showed no electromyographic activity. Three of 11 abductors of the little toe showed no activity while 7 more showed ± or doubtful activity. In several cases there was marked activity in abductor hallucis and this was found to be due to "digging in" of the great toe. This activity was more or less abolished immediately when the subject straightened his toe.

Physical examination. Careful examination of the feet revealed that 13 of the men had normal feet with arches of medium height, 2 had bilaterally low arches with slight valgus of the heel, and 2 had moderately flat feet with moderate valgus.

Nine of the 16 women had normal medium or high arches; 4 had normal low arches with no valgus of the heel and no history of trouble with the feet; 3 had low arches with slight valgus.

TABLE II.—FREQUENCY OF TYPES OF ELECTROMYOGRAPHIC ACTIVITY IN THREE INTRINSIC MUSCLES OF THE FOOT DURING RELAXED STANDING AT EASE

	Types of tracings, No.				
	++	+	±	o	Total
Abductor hallucis	1	o	2	9	12
Abductor digiti minimi	o	1	7	3	11
Flexor digitorum brevis	o	2	o	7	9

There was no consistent significant relationship between the types of feet and the types of activity in any muscle.

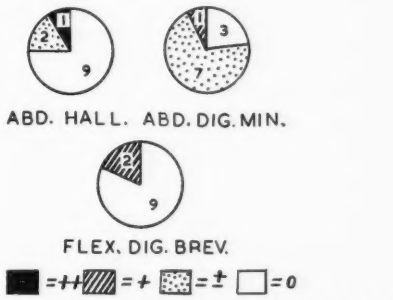

Fig. 3. Frequency of types of electromyographic activity in three intrinsic muscles of the foot during relaxed standing at ease.

DISCUSSION

It now seems to be beyond controversy that tibialis anterior, peroneus longus, and the intrinsic muscles of the foot play no important active role in the normal static support of the long arches of the foot. Our figures show that these muscles are completely inactive electromyographically in many normal individuals while standing. Smith came to the same conclusion after examining 6 subjects who all showed electromyographic quiescence during standing.

Although this investigation of predominantly normal feet showed no obvious relationship between types of feet and the types of activity in the muscles concerned during standing, no attempt is made to suggest that the muscles play no role in the abnormal flat foot. Furthermore, we are not dismissing the role of these muscles in the maintenance of the arch during locomotion. Indeed, the intrinsic muscles of the foot are always very active electromyographically when one rises on the toes to even the slightest degree.

In so far as the muscles of the leg are concerned the present results which show a biologic range of activity are not in accord with some of the findings of Smith, Joseph and Nightingale, and Åkerblom. We find that in the relaxed standing at ease position, there is activity in some individuals in the tibialis anterior and peroneus longus and that this can be abolished easily by unusual and varying stances or by the removal of weight from the limb. The disagreement probably stems largely from our use of the more sensitive unipolar needle electrode rather than simple skin electrodes. We are satisfied that the needle when properly inserted acts neither as a stimulator nor as an inhibitor of action potentials.

Joseph and Nightingale were concerned with soleus, gastrocnemius, and tibialis anterior. In 12 subjects they found continued activity in every soleus and in 7 gastrocnemii, but none in tibialis anterior. Since their original paper they have added to their series with no change in their conclusions.

The increased activity in all three of the muscles of the leg when high heels are worn may seem to be due to the element of instability introduced by the posture. But it will be noted that gastrocnemius and peroneus longus are involved and that tibialis anterior is not affected to any great extent. In another series of experiments we have found that peroneus longus is markedly active in plantar flexion of the ankle. It appears, then, that the wearing of high heels shifts the center of gravity forward to a new position in many women with a resultant increase in the activity of gastrocnemius and peroneus longus. Unfortunately, we have not done studies on the center of gravity and only on analyzing the data was this conclusion made.

SUMMARY AND CONCLUSIONS

Three muscles of the leg (tibialis anterior, peroneus longus, and the lateral head of gastrocnemius) and three intrinsic muscles of the foot (abductor hallucis, abductor digiti minimi, and flexor digitorum brevis) were studied electromyographically.

A unipolar needle electrode paired with a ring-shaped skin electrode was used according to Jasper's technique.

The muscles of the leg were studied in 17 men and 16 women. The women were tested both while barefooted and while wearing high heels. The intrinsic muscles of the foot were examined in a total of 14 persons.

A summary of the data is presented.

Tibialis anterior, peroneus longus, and the intrinsic muscles of the foot play no important role in the normal static support of the long arches of the foot. This is based on the finding that many if not most of the subjects showed inactivity in these muscles while standing.

All six muscles examined showed a biologic range of activity rather than a specific single type of activity in all persons. This range was from complete electromyographic inactivity in some to continuous activity in others.

In the men, gastrocnemius was active in a far greater proportion of subjects than were the other muscles. In the women, when they were barefooted, there was no great difference between the degrees of activity of the muscles of the leg. On the other hand, when high heels were worn the activity increased markedly in gastrocnemius and peroneus longus. A shifting forward of the center of gravity may explain this finding.

There was no obvious correlation between the electromyographic findings and the types of feet.

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LOCAL AMBULATORY TREATMENT OF CHRONIC LEG ULCERS WITH HYALURONIDASE, PLASMINOGEN, AND ANTIBIOTICS

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CHRONIC granulating leg ulcers are familiar to all physicians. The subjective misery and financial burden they inflict upon the patient are dishe tening. The economic and physical strain th place upon the outpatient department cli s and practitioners' offices is consider-ab Caring for these ulcers is a tedious ch e for the patient and physician alike. The pa nts object because of the length of time of erapy, the restriction of activity, and the pai common during the course of therapy. Be use the life span of our population has bee and is being extended, chronic ulcer patie s will represent an even greater problem. I patient facilities even for the severe cases are for the most part, difficult to obtain. Ma y ambulatory methods of treating these ulc s have been described. One of the simple has been the Unna paste or gelatin boot. Application of these boots is a time-consuming procedure which taxes the facilities of the clinics and physicians' offices. They are subjectively objectionable because of discomfort, malodor, and softening during the summer months. More recently the use of streptokinase-streptodornase, as described by Tillet and associates, and trypsin, as described by Reiser and Madden and their associates, has been added to the therapeutic armamentarium. Hyaluronidase and antibiotics alone have been used. No one method has been satisfactory. This study using a combination of enzymes and antibiotics for the local, ambulatory treatment of these lesions is presented.

MATERIALS

Plasminogen—37.5 milligrams per 1,000 cubic centimeters, prepared from fraction III of human plasma by a method previously reported (1), and activated with SK-SD

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Streptokinase-streptodornase (SK-SD)—100,000 units of SK, 25,000 units of SD (varidase) dissolved in 10 cubic centimeters of sterile solution—0.25 cubic centimeter of this solution added to each 10 cubic centimeters of plasminogen

Hyaluronidase—1,500 turbidity reducing units dissolved in 10 cubic centimeters of sterile solution

Bacitracin—500 units per cubic centimeter

Terramycin IV—25 milligrams per cubic centimeter

Methocel—a water soluble methylcellulose base

Sixteen patients with chronic ulcers were previously treated by routine methods for long periods of time in our clinic and elsewhere without success. Many of these patients had received surgical treatment for varicose veins. One patient (Case 10) had consistently refused surgery. All patients had good arterial pulses in their feet. Fifteen were treated entirely as outpatients and the remaining patient (Case 2), an 18 year old male, was an inpatient who was being prepared for skin grafting.

METHODS

These lesions were regarded primarily as the result of stasis changes, and, therefore, surgery and all measures capable of reducing this stasis such as elevation, diet, and elastic bandages were utilized. The general management of these patients was not changed. As before, the involved area was first washed with *p*Hisoderm with hexachlorophene solution (*p*HisoHex). Then, instead of applying the scarlet red, gentian violet, hydrophilic furacin or other ointments, plasminogen or hyaluronidase with or without antibiotics was used. The treatment of the wound was then completed with a sterile dressing and an ace bandage.

The first patients were treated with liquid preparations in the outpatient department (Table I). They received treatments 5 days a week for an initial observation period, and thereafter 3 times a week. The enzyme and antibiotic in solution were placed upon the

TABLE I.—CHRONIC LEG ULCERS TREATED LOCALLY WITH LIQUID PREPARATIONS OF ENZYMES AND ANTIBIOTICS IN THE OUTPATIENT DEPARTMENT*

Patient	Description							Treatment		Results			Comments
Case No. Sex Age	Type (etiology)	Duration	Previous treatment	Size and location	Pain	Cellulitis	Fibrosis	Medication	Duration	Size	Pain	Follow-up	
1 F 12	Trauma and infection	8 wks.	7 wks. of soaks, and antibiotics in NYHOPD	Midtibia 3.0×2.5 cm.	++++	++	0	H & T	5 wks., q.d.	Closed	Absent in 1 wk.	5 mos., no recurrence	Marked pain relief and closed in 5 wks. No progress was being made in 7 previous wks. of usual NYHOPD Rx
2 M 18	Trophic	4 wks.	Soaks and antibiotics by LMD	Base of toe 5.0×3.0 cm.	0	Base necrotic	0	P H & T	5 days, q.d.	Pinch grafted	—	5 mos., no recurrence	Dirty base prepared for pinch grafts rapidly
3 F 32	Stasis (large V.V.)	8 wks.	Injections, hydrophillic ointment in NYHOPD	L.M.M. 1.0×1.5 cm.	++++	++++	+	H & T	3½ wks., q.d.	Closed 50 per cent	Absent in <1 wk.	5 mos., no recurrence	Two months usual NYHOPD Rx unsuccessful preparation for phlebectomy. In <1 mo. on enzymes, pain relieved, cellulitis cleared, phlebectomy done. Closed 2 wks. later
4 M 56	Stasis (no V.V.)	8 mos.	LMD 8 mos., Unna boot, NYHOPD 4 days	Above R.M.M. 4 ulcers, largest 2.5×1.0 cm.	++++	++++	+	H	6 wks., q.d.	Closed	Absent in 1 wk.	7 mos., no recurrence	Has been working as an inspector, walking all day, since discharge
5 M 68	Osteomyelitis and stasis	Intermittently, 6 yr. Presently, 6–7 mos.	LMD 6 mos. NYHOPD, 1 mo. Hydrophillic ointment	Above R.M.M. 3 ulcers, largest 3.0×4.0 cm.	0	Brawny	+++	H & T	7 wks., q.d., then 6 wks., q.o.d.	Closed	—	5 mos., no recurrence	Successful closure in an ulcer with an underlying osteomyelitis
6 F 43	Stasis (no V.V.)	Intermittently, 13 yr.	Bilateral phlebectomies, 3 mos. previously	L.M.M. (2) a) 1.5×1.5 cm. b) 2.0×2.0 cm.	++++	++	++++	P & T H & T	3 wks., q.d. 4 wks., q.d. then 5 wks., q.o.d.	Closed	Absent in 1 wk.	4 mos., no recurrence	Treated ulcers closed while controls remained open, red, painful, despite greater fibrosis in treated ones (controls, Rx'd with enzymes later, closed more rapidly than ones treated originally)
				L.L.M. 1.5×1.5 cm. R.M.M. 1×1 cm.	++++ ++++	++	0	Controls-hydrophilic ointment, q.d.		Remained open	Remained +++	—	
7 F 64	Stasis (bilateral V.V.)	Intermittently, 17 yr.	NYHOPD: Injections, boots, 1951; phlebectomies refused	L.M.M. 1.0×1.5 cm.	++	0	++++	P & T P H	5 days, q.d. 11 days q.d. 4 mos. q.o.d.	Closed	Absent in 2 wks.	5 mos., no recurrence	Boots closed this ulcer in same length of time, 2 yrs. ago. Patient disliked boots and was happier, more comfortable on present Rx
8 M 66	Stasis (no V.V.)	Intermittently, many years Presently: 2 yr.	Outside Rx boots NYHOPD: Scarlet red, etc.	Lower tibia 2.0×8.0 cm.	0	++	++++	H & T H	3 wks., q.d., then 3 mos. q.o.d. 3 mos., q.o.d.	Decreased, now is 7.0×2.0 cm.	—	Currently being treated	Size decreased. Delayed by local reaction to topical terramycin and markedly fibrotic base which enzymes penetrated poorly. Local reaction gone, closing slowly

TABLE I.—CHRONIC LEG ULCERS TREATED LOCALLY WITH LIQUID

TABLE I.—CHRONIC LEG ULCERS TREATED LOCALLY WITH LIQUID PREPARATIONS OF ENZYMES AND ANTIBIOTICS IN THE OUTPATIENT DEPARTMENT*

Patient	Description					Treatment			Results			Comments
Case No. Sex Age	Type (etiology)	Duration	Previous treatment	Size and location	Pain	Cellulitis	Fibrosis	Medication	Duration	Size	Pain	Follow-up	
9 F 68	Stasis (no V.V.)	Intermittently, 15 yr.	Boots 1938. Phlebectomy NYHOPD 1950	L.M.M. 4.0×7.5 cm.	+++	Base necrotic	++++	P & T H & T	3 wks., q.d. 1 mo. q.d., then 3 mos., q.o.d. 4 mos., q.o.d.	Slightly decreased, 2.5 ×5.5 cm.	Absent in 2 wks.	Currently being treated	Slow improvement. Pain relieved promptly. Markedly fibrotic base, poorly penetrated by enzymes
10 F 65	Stasis (massive V.V.)	Intermittently, 10 yr.	Boots, ointments, NYHOPD. Phlebectomies refused	L. tibia (2) a) 3.0×5.0 cm. b) 3.0×2.0 cm.	0	+++	++	H	3 wks., q.d. 2 mos., q.o.d.	a) 2.0×4.0 cm. b) Closed	—	Signed release. Treatment discontinued	Needed phlebectomies badly. Treated ulcers always cleaner than controls (Controls later treated with enzymes and cleared of cellulitis)
				R. tibia (2) a) 3.0×2.0 cm. b) 1.0×1.0 cm.	0	+++	++	Controls-hydrophilic ointment, q.d.		Remained open	—		

Key: H, Hyaluronidase; P, Plasminogen; T, Terramycin; B, Bacitracin; NYHOPD, New York Hospital Outpatient Department; LMD, Local physician; M.M., Medial malleolus; L.M., Lateral malleolus; V.V., Varicose veins.

*Case 2 received liquid preparations but was treated as an inpatient.

ulcer for 30 minutes. Then a gauze pad 2 by 2 inches saturated with the solution was applied over the ulcer and held in place with a strip of vaseline gauze, dry sterile dressing, and ace bandage. This was a cumbersome, time-consuming method, but necessary to assure an adequate period of drug contact when the liquid preparation was used, before the patient was ambulated. At the outset of this study, alternate cases were treated with: (a) plasminogen; (b) plasminogen plus terramycin; (c) hyaluronidase; and (d) hyaluronidase plus terramycin. After the initial period, the final routine of dressings was hyaluronidase with or without terramycin, 3 times a week.

The last 6 patients (Table II) were given the medications in a water soluble base to take home. This ointment was to be kept refrigerated and applied as daily dressings by the patient at home. These patients were then seen weekly. For the first week the ointment they received contained plasminogen, with bacitracin in 4 instances and with terramycin in 2. The plasminogen was used to clear up the exudate. Subsequently, hyaluronidase with the antibiotic in ointment was used for the next 1 or more weeks until the cellulitis cleared, and then hyaluronidase in ointment alone was applied.

RESULTS

Since local conditions in these ulcers vary so much, it was believed that using patients themselves for controls was more accurate than using a similar series of cases. Accordingly, comparisons were made in the individual patient between previous treatments and the present regimen and between 2 ulcers, 1 treated and 1 not treated, in the same patient. These findings are tabulated in Tables I and II.

In patients with control ulcers on the same or opposite leg, those treated by this method became cleaner, less painful, and all regressed to a greater or lesser extent, while the controls remained painful, angry looking, and about the same size.

The patients in this series had been seen and treated in our outpatient department and elsewhere for varying periods of time without success. This method of enzymatic-antibiotic

TABLE II.—CHRONIC LEG ULCERS SELF-TREATED LOCALLY WITH BASE PREPARATIONS OF ENZYMES AND ANTIBIOTICS AT HOME

Patient	Description							Treatment		Results			Comments
Case No. Sex Age	Type (etiology)	Duration	Previous treatment	Size and location	Pain	Cellulitis	Fibrosis	Medication	Duration	Size	Pain	Follow-Up	
11 M 68	Stasis (few V.V.)	Intermittently 15 yr. Presently 1 wk.	Phlebectomy NYH 10 yr. ago. Hydrophilic oint. 1 wk.	4 above L.M.M. up to 2.0×3.0 cm., 1 over L.L.M. 1 over tibia	++++	++++	+++	P & T H & T H	1 wk., q.d. 1 wk., q.d. 2 wks., q.d.	All closed	Absent in 1 wk.	4 mos. no recurrence	Prompt pain relief. All 6 ulcers closed in 4 wks.
12 F 54	Stasis (no V.V.)	Intermittently 18 yr. Presently 8 mos.	Gentian violet and ace bandage by LMD, 8 mos.	L.M.M. (2) a) 2.0×2.5 cm. b) 1.8×2.5 cm.	+++	+++	++	P & B H & B	2 wks., q.d. 3 wks., q.d.	Both closed	Absent in 2 wks.	3 mos., no recurrence	Completely closed in 5 wks. Previously unsuccessfully treated by LMD for 8 mos.
13 M 63	Stasis (few V.V.)	Intermittently 13 yr. Presently 2½ yr.	Outside Rx: Ligations, x-ray Rx, 10 yr. ago. NYHOPD: 2½ yr. boots. etc.	R.M.M. 5.0×7.0 cm.	++++	++++	++	P & B H & B	1 wk., q.d. 13 wks., q.d.	Closed	Absent in 2 wks.	1 mo., no recurrence	Low ligations, x-ray Rx closed this ulcer many years ago. Recurred 2½ yr. ago. Continuous NYHOPD Rx since then unsuccessful. Present Rx relieved pain, cleared infection promptly, encouraged rest. Closed in 14 wks.
14 M 52	Stasis (no V.V.)	Intermittently 25 yr. Presently 1 yr.	Ointments & grafting. Phlebectomy NYH, 1951	L. low leg a) 3.0×4.3 cm. b) 4.0×1.5 cm. c) 4.0×3.5 cm.	++++	++++	++++	P & B H & B	5 days, q.d. 12 wks., q.d.	a) 2.5×4.0 cm. b) 3.4×1.5 cm. c) 3.0×2.2 cm.	Absent in 3 wks.	Currently being treated	Marked fibrosis, previously skin grafted. Reduction in size, pain on present Rx, while keeping on job as a supervisor, walking most of day
15 F 30	Stasis (moderate V.V.)	Intermittently 4 yr.	NYHOPD Rx: 5 wks. of aureomycin ointment	Above L.M.M. 3.0×3.0 cm.	++++	++++	+	P & T H & T	1 wk., q.d. 4 wks., q.d.	Slightly decreased	Marked pain relief in 2 wks.	Currently being treated	Ulcer had grown slightly larger, more painful on 5 wks. of usual NYHOPD Rx. In 5 wks. on present Rx, size decreased, pain gone, cellulitis cleared. Ready for phlebectomy
16 M 68	Stasis (moderate V.V.)	Intermittently 12 yr. Presently 3 mos.	NYHOPD Rx: 3 mos. of aureomycin ointment	L. lower tibia 2.0×1.5 cm.	o	++++	++	H & B H	2 wks., q.d. 2 wks., q.d.	Closed	—	2 wks., no recurrence	A fiery red cellulitis, little recent improvement in size noted after 3 mos. of usual NYHOPD Rx. On enzyme-antibiotics, cellulitis cleared in 1 wk. ulcer closed in 4 wks. To be admitted for phlebectomy

treatment was successful where conventional therapy had failed, or it worked more rapidly than conventional therapy, in 12 of the 16 cases. In the remaining 4 cases (Cases 8, 9, 14, and 15) in which the ulcers did not close after a satisfactory period of treatment, cellulitis was rapidly reduced and pain eliminated in all. Two of these ulcers occurred in patients (Cases 8 and 9) in whom the fibrosis was so dense that very little enzyme solution penetrated the ulcer base.[1] The other 2 failed to heal because phlebectomies were needed. One patient (Case 10), a 65 year old female had massive varicose veins. She consistently refused surgery and was finally released. The fourth patient (Case 15) was a 30 year old female who had moderate varicose veins. She had been treated for 5 weeks in our clinic. During this period, the ulcer had increased slightly in size and the pain remained severe. She had a 3.0 by 3.0 centimeter ulcer when first accepted for this study. During the 5 week period in which she received enzymes and antibiotics, the ulcer decreased slightly in size, and the cellulitis and pain disappeared in about 3 weeks. She is ready for phlebectomy and should have a good result, similar to that of the patient in Case 3.

The most remarkable benefit came in cases in which local cellulitis and edema had caused the intense pain that irritation of the cutaneous nerves can produce. Many were unable to sleep and had no relief from analgesics. Pain prevented many from working and kept them miserable. In every one of these cases the edema and cellulitis were reduced within 5 to 14 days. The skin changed from fiery red to pink in this short period. The subjective relief from pain was dramatic, which probably explains why these patients were willing to come back so regularly. Relief from this constant, unrelenting pain produced a most grateful group of patients. They remained comfortable during their entire course of therapy.

This regimen proved efficacious in healing a stasis ulcer with an underlying chronic osteomyelitis. It also permitted a rapid preparation for surgery, in 1 case for pinch grafting and in 3 others for excision of varicose veins. This method has virtually eliminated the use of Unna paste boots in our clinic because enzymes, antibiotics, and ace bandages appeared to work as fast or faster, and patients were spared the discomfort and pain of boots. This also represents a tremendous saving in nurse-hours and clinic space, for it has been estimated that 30 to 40 minutes are spent by the nurse, and the clinic aide holding the patient, for the complete application and drying of each boot. A complete dressing, using medications in the base, requires only a few minutes.

A local drug reaction was noted in 1 case. This consisted of the development of local erythema in a patient on topical terramycin for 3½ months, which regressed upon cessation of terramycin administration. In retrospect, it was believed that continuing the antibiotic for so long a time was a mistake. First, there is the danger of a local reaction, and secondly antibiotics are probably efficacious primarily in the acutely infected stage which was cleared up quickly in all cases.

In the last 6 patients treated with the medications in a water soluble base and seen weekly, the results were as good, indeed better in 4 cases than those in the patients who received daily treatments with liquid medications in the hospital outpatient department. It is quite possible that using a base allows a slower absorption of the medication over 24 hours and, therefore, provides a more uniform and prolonged action than the liquid preparation. It is certainly a more economical method, both as to time spent and clinic space utilized, and offers the possibility of treating many more patients.

DISCUSSION

With the development of a method of purification of human plasminogen (1), the basis of the fibrin-lysing system in exudates which streptokinase catalyzes, a direct potent physiologic enzyme for the débridement of wounds was made available. This has been shown by in vitro studies (1) to be an active fibrinolytic enzyme and relatively nontoxic in vivo(2) in animals. Furthermore, it remains stable at room temperature for over 12 hours.

[1]The possibility of injecting a sterile solution of the enzyme subcutaneously might be efficacious in such cases but was not tried in these instances.

Débridement alone did not seem to be sufficient for healing of the old chronic ulcers, and indeed it was soon noted that, although very clean, they did not heal rapidly. Hyaluronidase was next considered and seemed a logical choice in theory, first because of its effect on the ground substance of tissue and, secondly, since it increases the spread of substances introduced into the tissues, it seemed logical to expect that it would also produce diffusion of edema. The effect of both of these factors is to reduce local tissue tension and thereby increase the spread of tissue fluids bearing oxygen, nourishment, and antibiotics into the fibrotic tissues underlying the ulcers.

Since many of these cases were referred for treatment during an acutely painful and infected stage, antibiotics were added to combat the local cellulitis. By adding the antibiotic to these enzymes, two of the major objections to local antibiotic therapy were overcome. That is, tissue exudates which have been considered to inactivate antibiotics and to prevent direct contact between the agent and wound were débrided by the plasminogen. Hyaluronidase permitted the penetration of the antibiotic into the deeper lymphatic and granulation tissue to combat organisms there. It has been shown by Som and associates that hyaluronidase increased the absorption of local penicillin across mucous membranes by two or three times the amount absorbed when penicillin alone was used. Antibiotics alone have been shown to be efficacious in the treatment of local infection in leg ulceration secondary to arterial insufficiency. Observation of patients in our study suggested that antibiotics are most efficacious in the initial treatment while the wound is obviously infected.

When debris and exudate are present, plasminogen is more effective than hyaluronidase. When the wound is cleaned up or when there is no necrotic debris initially, hyaluronidase offers a more direct attack by (a) permitting edema to diffuse more rapidly and (b) by increasing the local circulation. Thus a continuous cycle of decreasing edema and improved circulation may be established and perpetuate each other.

The most efficacious method, therefore, is débridement with plasminogen combined with antibiotics for a short period initially. Thereafter hyaluronidase with antibiotics should be used while cellulitis persists and then hyaluronidase alone, to promote epithelialization. In this manner, local edema and cellulitis may be cleared most efficiently and maximal local circulation may be achieved most rapidly.

CASE REPORTS

Of the 16 patients whose cases are summarized in Tables I and II, 14 represent the usual stasis ulcers but 2 instances are in younger people.

CASE 1. Y.W., NYH 630146, a 12 year old female, had a 3.0 by 2.5 centimeter ulcer over the upper one-third of the tibia which resulted from scratching a furuncle. She was treated in our own clinic by the usual measures with soaks, hydrophilic ointment, and other ointments including terramycin for 7 weeks. When seen following this treatment she still had heaped-up fiery red granulations which were so extremely painful that she was forced to sob whenever the dressings were changed. Furthermore, during these 7 weeks, no headway had been made in decreasing the size or the pain of the ulcer. The base of the ulcer was clean and she was started on daily hyaluronidase and terramycin solution. In 3 or 4 days the granulations were pink. There was absolutely no pain in about 1 week, and the ulcer closed completely in 5 weeks.

CASE 2. L.R., NYH 653711, an 18 year old male, had glove anesthesia over the entire large toe (from the metatarsal interphalangeal joint distally) following a digital block to remove an ingrown toenail. He subsequently developed a large triangular shaped ulcer over the volar surface of this toe which was treated without improvement with soaks and antibiotics for about 1 month by his local physician. When seen the base was full of necrotic debris. He was hospitalized and started on plasminogen, hyaluronidase, and terramycin solution. By this treatment the base of the ulcer was cleaned out within 4 or 5 days, and pinch grafts were successfully applied.[1]

The remaining patients were generally older or had longer histories of stasis ulcers.

CASE 3. L.S., NYH 597763, a 32 year old female, had had 5 pregnancies as well as bilateral varicose veins for 13 years. During the past 5 years she had had several stasis ulcers, some of which had remained open for years. She worked as a nursing aide at the New York Hospital and was on her feet constantly.

[1]It was believed that this lesion would have taken many more days to clean up with the usual saline or Dakin's irrigations, and, therefore, that the present treatment offers the possibility of a more rapid method of preparing dirty wounds for surgery or discharge. Wound infections, for example, may be cleaned up more rapidly for secondary closure or earlier outpatient care.

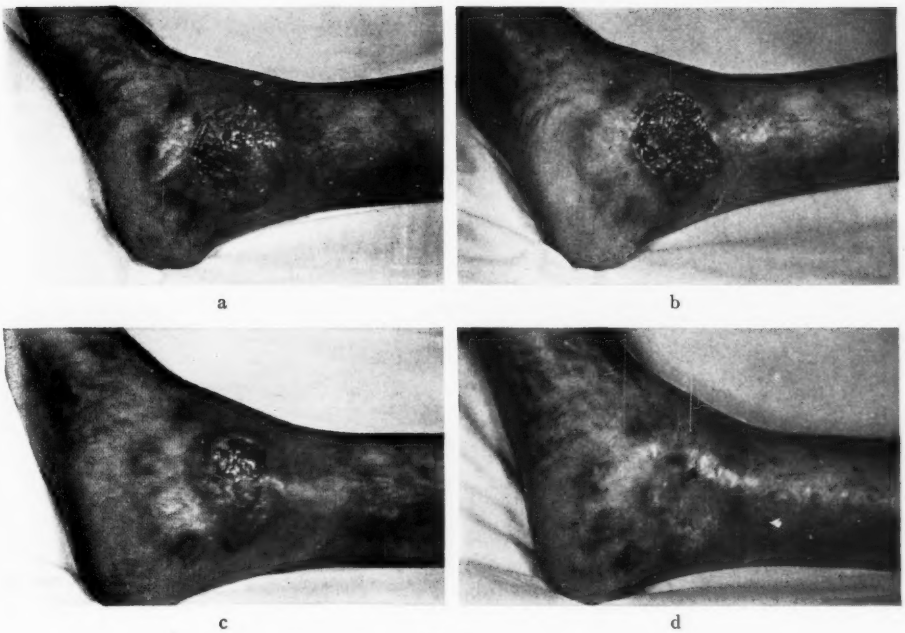
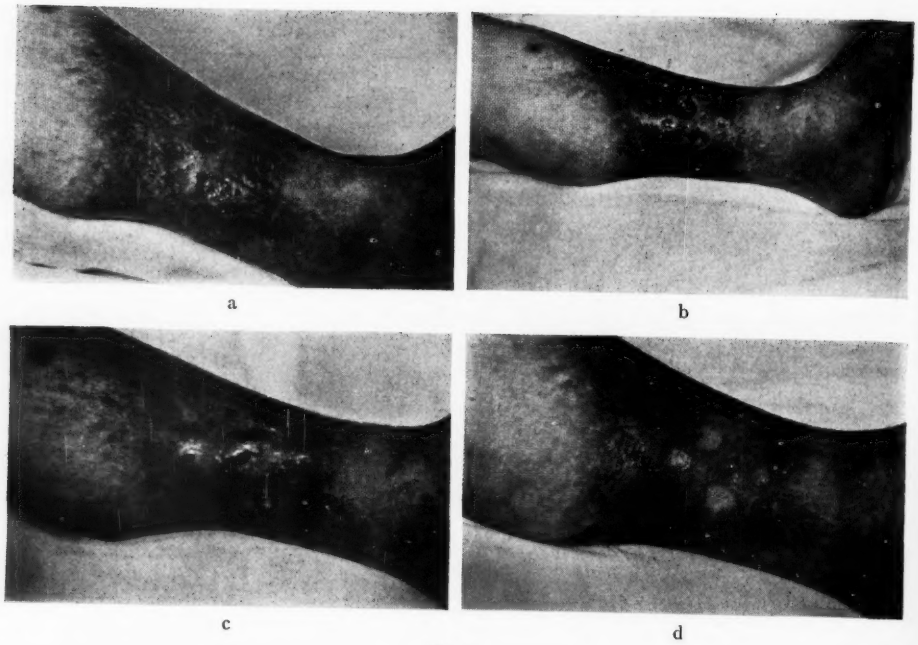


Fig. 1.

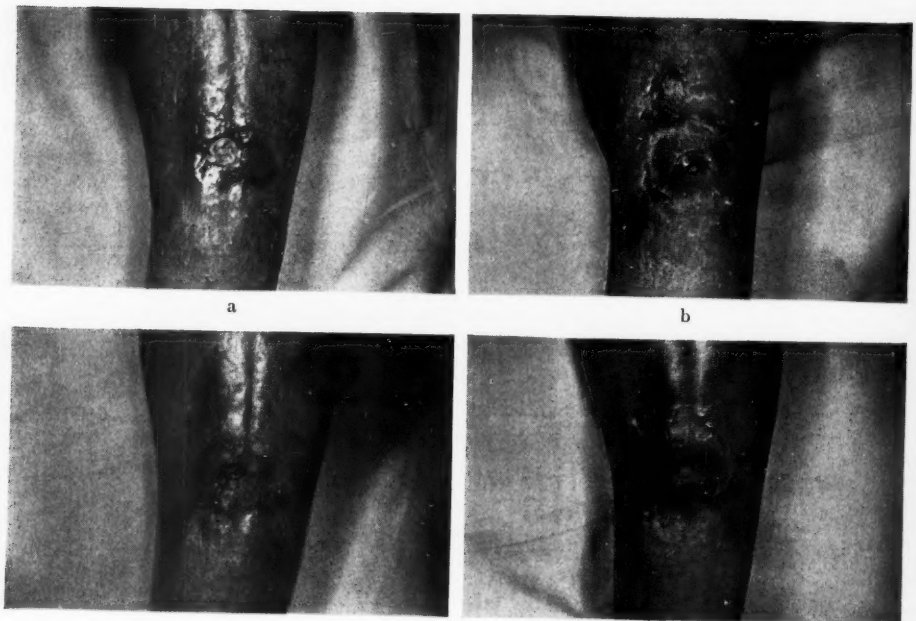
Fig. 1. Case 13. a, Before present treatment was begun. b, After 1 week of treatment with plasminogen and bacitracin. c, After 3 weeks of treatment with hyaluronidase and bacitracin, during the fourth week. d, After 12 weeks of treatment with hyaluronidase and bacitracin, totalling 13 weeks of treatment. (Final illustration, taken 9–24–53, too dark for publication.)

Local Ambulatory Treatment of Chronic Leg Ulcers with Hyaluronidase, Plasminogen, and Antibiotics.—I. Robert Spier and Eugene E. Cliffton.



a b c d

Fig. 2.



a b c d

Fig. 3.

(*Legends on opposite page.*)

(This case was gratifying because it illustrates a planned attack on this problem.) The present ulcer 1.0 by 1.5 centimeters over the medial malleolus had developed following scratching of this area 2 months previously. She was seen in our outpatient department then and started on the conventional treatment with a plan to admit her for surgery for her varicose veins when the cellulitis and ulcer had healed sufficiently. Despite 2 months of this treatment she still had a fiery red cellulitis and edema in the surrounding area, 5.0 centimeters in diameter. She complained of severe pain for which she was taking 2 acetylsalicylic acid-phenacetin-caffeine tablets every 3 or 4 hours with little relief. The pain of each daily dressing was especially severe and persisted for several hours. She was started on daily hyaluronidase and terramycin solution and given an admission slip for 1 month hence. The pain, 4 plus at the start of enzyme therapy, ceased completely in less than 5 days as the cellulitis resolved in this period. (The brawny dermatitis remained, of course.) Within 21 days the entire area was dry and cool, and the ulcer half closed. She was admitted, and a bilateral saphenous ligation and stripping operation was performed 1 month after the onset of this treatment. She was discharged 3 days following surgery to the outpatient department where she was again started on hyaluronidase and terramycin. The ulcers closed 2 weeks later.[1]

CASE 4. J.B., NYH 199194, a 56 year old male, had 4 ulcers on his leg, the largest of which was 2.5 by 1.0 centimeter. He had had no history of trauma, no varicose veins, and had good pedal pulses. There was some dependent rubor of the feet. He had had these ulcers for 8 months and had 4 plus pain, which kept him awake at night, and 3 plus erythema. He was treated with hyaluronidase solution daily because the ulcers were fairly clean, and all ulcers closed within 6 weeks. He was relieved of pain in 1 week. He has been followed 7 months and has had no breakdown. He wears an elastic stocking and has been on his feet all day working as an inspector during these 7 months.

CASE 5. A.P., NYH 180992, a 68 year old male, had fractured his right tibia 6 years previously, and the fracture had been treated by open reduction at another clinic. He subsequently developed ulcers in the incision which opened and closed intermittently during this period. His present ulcers included 3 shallow ones, the largest of which was 3.0 by 4.0 centimeters. There were extensive brawny changes over the entire lower leg. These ulcers had been open about 7 months. Roentgenograms showed a chronic osteomyelitis. He was started on hyaluronidase and terramycin solution, daily for 7 weeks and then every other day. The ulcers closed, and he was discharged following a total of 13 weeks of treatment. The possibility of treating chronic leg ulcers with an underlying osteomyelitis with these medications is, therefore, presented.

CASE 6. E.W., NYH 648485, a 43 year old obese female, had had 4 pregnancies and ulcers on both legs intermittently for 13 years. She had had bilateral phlebectomies 3 months previously in an effort to heal these ulcers. They persisted, however, and she entered the clinic with ulcers of the left leg over both malleoli, and 1 over the right medial malleolus. Her pain was 4 plus. She offered the possibility of good controls. On her left leg there were 2 ulcers over the medial malleolus, 1.5 by 1.5 centimeters and 2.0 by 2.0 centimeters in size, in a surrounding area of 6.5 centimeters of fibrotic skin. Over the left lateral malleolus there was an ulcer, 1.5 by 1.5 centimeters with some cellulitis but no fibrosis. This smaller left lateral ulcer and the right leg ulcer, 1.0 by 1.0 centimeter with a moderate amount of cellulitis and no fibrosis, were used as controls and received hydrophilic ointment. The treated ulcers received plasminogen and terramycin solution for 3 weeks, and then hyaluronidase and terramycin solution. In 3 months the treated ulcers healed completely, while the controls, which were smaller and less fibrotic to start with, remained open, were very painful with persistent cellulitis. The controls were then treated with hyaluronidase and terramycin and closed in 5 weeks. They healed more rapidly because the skin in these areas was much less fibrotic.

CASE 11. F.H., NYH 153451, a 68 year old male, had been treated in our clinic for 1 week with hydrophilic ointment. He had had a phlebectomy on this leg at the New York Hospital 10 years ago. At the time he was seen, he had 6 ulcers on his left leg. There were 4 ulcers over the medial aspect about 4 centimeters above the medial malleolus which ranged in size to a maximum of 2.0 by 3.0 centimeters. He had 1 ulcer over the tibia anteriorly and 1 ulcer over the lateral malleolus, about 2.0 by 1.0 centimeter in size. These ulcers were extremely painful and kept him awake at night. When seen, the ulcers were filled with necrotic exudate, and there was very marked surrounding cellulitis. A preparation of plasminogen and terramycin was made up in a water soluble base and was given to the patient to be applied as a daily dressing at home. He used this for 1 week and then

[1]This patient illustrates a much more rapid preparation for surgery on an outpatient department basis where the conventional treatment was slow and no real progress was shown. She also represents a case of marked subjective relief and comfort during the course of therapy.

Fig. 2. Case 11. a, Before present treatment was begun. b, After 1 week of treatment with plasminogen and terramycin. c, After 1 week of treatment with hyaluronidase and terramycin, during the second week. d, After 2 weeks of treatment with hyaluronidase alone, totalling 4 weeks of treatment.

Fig. 3. Case 16. a, Before present treatment was begun. b, After 1 week of treatment with hyaluronidase and bacitracin. c, After 2 weeks of treatment with hyaluronidase and bacitracin, during the second week. d, After 2 weeks of treatment with hyaluronidase alone, totalling 4 weeks of treatment.

returned to the clinic. At this time, he reported complete relief from pain and was again able to sleep at night. When seen after this first week, his ulcers had cleared up considerably and were much more delineated. Therefore, a preparation of hyaluronidase with terramycin in the base was made and given to the patient for daily dressings at home. After 1 week of this treatment, 3 of the 4 medial ulcers had healed almost completely and the fourth one, the largest, was reduced to one-half its size. It measured 2.0 by 1.0 centimeter. The left lateral ulcer was reduced to 1.0 by 0.5 centimeter, and the anterior ulcer was practically closed. He was given a fresh unit of hyaluronidase in the base for home applications. By the end of the third week all ulcers had closed except for a 0.5 centimeter residual opening of the largest ulcer which closed by the next week, 1 month after the onset of this regimen.

SUMMARY

A rapid ambulatory method of local treatment using enzymes and antibiotics to débride, combat cellulitis, improve local circulation, and promote epithelialization in chronic ulcers is presented as an adjuvant to surgery and other general measures which reduce stasis. Hyaluronidase promoted epithelialization much more rapidly, and plasminogen was very valuable in the preliminary débridement of ulcers with necrotic bases. Antibiotics added to these enzymes helped combat the local cellulitis. This procedure has been successful in many cases in which usual methods in our clinic have failed.

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SARCOMAS OF THE SOFT SOMATIC TISSUES IN INFANTS AND CHILDREN

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MALIGNANT tumors destroy the lives of more infants and children than do most other diseases including tuberculosis, heart disease, and poliomyelitis. Studies have been conducted pertaining to the etiology and treatment for practically all pathologic processes in the young human with the exception of cancer. Oncology in children has been neglected because of a number of misconceptions pertaining to this disorder. Among these are: (1) Cancer is so rare that it does not warrant extensive investigation. (Although relatively infrequent it nevertheless constitutes the major threat to the life of the developing infant and child.) (2) It is universally fatal, therefore, a pessimistic attitude prevails. (It shall be shown that this concept is entirely erroneous.) (3) Malignant tumors in infants and children have such a proclivity to growth and propensity to metastasize that they resist every effort at local control. (Although certain tumors of childhood do tend to grow more rapidly than do their counterparts in the adult, proper therapy can control most childhood neoplasms. Contrariwise, certain neoplasms in children may present a highly malignant histologic appearance but behave benignly from a clinical standpoint, e.g., melanomas, certain liposarcomas.) (4) Cancer in childhood represents an end stage of a prenatal abnormality and at the time the cancer is noted clinically it is already widespread. (This concept is fallacious and most childhood neoplasms are localized when first discovered.) The list of misconceptions as well as others not listed serves to divulge a trend of thought which currently prevails concerning cancer in infants and children.

An understanding of the natural history of malignant tumors in childhood and their points of similarity and divergence from cancer in the adult would permit the development of therapeutic methods and offer scales for measuring prognosis. A critical evaluation of the efficiency of the therapeutic modalities utilized could then be made.

This report presents the results of an analysis of the clinical courses correlated with the histologic details of soft somatic tissue sarcomas of infancy and childhood. Methods of treatment are evaluated and end results presented.

INCIDENCE OF CANCER IN CHILDREN

Cancer, one of the greatest threats to the lives of the infant and child, is increasing in frequency. It is the third greatest cause of death in children from 1 to 14 years of age, being exceeded by accidental deaths and pneumonia (Table I), and the second foremost cause of death in youths between 5 to 14 years, being exceeded only by accidents. This high death rate is a rather recent development. For example, 20 years ago it was not even listed within the group of the 10 most frequent causes of death in children. It is believed that there has not been an absolute increase in the incidence of cancer in children but rather that the precipitous decline of the death rate from neonatal and infectious diseases focuses attention upon the frequency with which cancer kills babies and children.

Over 2,000 infants and children between the ages of 1 and 14 years died in the United States from cancer in 1947. In 1948, cancer, including leucemia, caused 7.3 per cent of all deaths of children between 1 and 14 years of age.

The causes of death in New York City for the year 1950 are presented in Table II. The breakdown is that of the New York City Department of Health Statistical Division. The high incidence of neoplastic deaths in children is evident.

TABLE I.—LEADING CAUSES OF DEATH FOR CHILDREN, AGED 1 THROUGH 14 YEARS, IN THE UNITED STATES IN 1947

Cause of death	No.	Per cent of all causes
All causes	33,344	100.0
Accidental deaths	10,731	32.2
Pneumonia	3,240	9.7
Cancer, including leucemia	2,490	7.5
Tuberculosis	1,328	4.0
Heart disease	1,131	3.4
Congenital malformation of cardiovascular system	920	2.8
Meningitis	823	2.5
Congenital malformation of nervous system	810	2.4
Diarrhea, enteritis	724	2.2
Appendicitis	700	2.1
Nephritis	668	2.0
Diphtheria	637	1.9

TYPES OF CANCER IN INFANTS AND CHILDREN

Unlike cancer in adults, carcinoma is very rare in children. Sarcomas, embryomas, and mixed tumors are most frequent. Of 219 malignant tumors reported by Steiner at Children's Memorial Hospital, Chicago, and the University of Chicago, only 1 carcinoma (of the liver, with juvenile cirrhosis) was encountered. At the Babies Hospital, New York, of 175 malignant tumors reported by Andersen, 11 were of mesodermal origin, 5 were teratomas, 10 were carcinomas, and 49 were of the nervous system. Although different institutions with selective criteria for admission may show certain variables of incidence and types of childhood cancer, it is established that sarcomas are by far the most frequent form of cancer in children. In Table III are correlated the chronologic and physiologic ages of man and listed are the most frequent neoplasms for the different age spans.

LOCATION OF TUMORS IN INFANTS AND CHILDREN

Benign tumors. In a series of 600 surgical specimens from infants and children Steiner noted 22 per cent were malignant tumors, 63 per cent were benign tumors, and 15 per cent were nonneoplastic.

The most frequent benign tumors were polyps, papillomas, and polypoid adenomas of such epithelial structures as the larynx, rectum, nose, and ear, and in decreasing frequency hemangiomas, dermoids, epidermoids, fibromas, lymphangiomas, and others.

Tumors of the connective tissue group (fibromas, lipomas, neurofibromas, lipofibromas, chondromas, and osteochondromas) rated third in order of frequency.

A finding of interest from the necropsy series is that benign tumors noted as an incidental finding during necropsies in adults are not seen in children. These include: uterine polyps and fibroids; adenomas of the thyroid, adrenal cortex, and kidney; adenomatous hyperplasia of prostate; polyps and polypoid adenomas of the colon; hemangiomas of the liver; fibroadenomas of the mammary glands; and papilloma of the urinary bladder.

Cancer. The tissues most frequently involved by cancer in children, as reported by Dargeon and associates, in order of decreasing frequency (over 1,700 cases of children's cancer of reported series) are: central nervous system in 370 cases; bones in 365 cases; eye and orbit in 235 cases; genitourinary system in 230 cases; lymphatic system in 204 cases; soft somatic tissue sarcoma in 144 cases; pharynx in 36 cases; skin in 31 cases; gynecologic in 25 cases; gastrointestinal tract in 21 cases; abdomen in 19 cases; miscellaneous in 18 cases; liver in 13 cases; salivary glands in 7 cases; lung in 5 cases; pancreas in 3 cases; and lip in 2 cases.

Sarcomas of the soft somatic tissues of children vary in incidence with the different reports from various hospitals.

GENERAL INCIDENCE OF SARCOMAS IN CHILDREN

At the Mayo Clinic, of 750 malignant tumors in infants and children reported by Helmholz, there were only 18 instances of sarcomas of the soft somatic tissues. Duzan (1876) reported on 183 tumors of infancy and childhood, and Picot (1883) reported 424 tumors of childhood. Neither reported on sarcomas of the soft somatic tissues.

Arey, reporting from the St. Christopher's Hospital for Children and Temple University

School of Medicine, Philadelphia, presented 62 malignant tumors in children observed during an 18 month period. The most frequent form was sarcoma of the soft tissues which comprised 18 per cent of all the childhood cancers.

Videbaek reporting from Denmark indicated that of 276 childhood cancers reported from 1942 to 1944 the most frequent were the lymphomas (30 per cent) while the second most frequent form was sarcoma of the soft somatic tissues (20 per cent).

Koh and associates reported that at the University of Michigan, 272 malignant tumors of children were recorded between 1943 and 1947, with only 12 instances of soft tissue sarcomas.

From the Boston City Hospital, Ritvo and associates reported 72 instances of childhood cancer during a 25 year period, and of these, sarcomas of the soft tissues comprised 9 per cent of their total experience. Scotti reported 8 sarcomas of the soft tissues of a total of 64 children observed at the New York Post-Graduate Hospital. Blacklock (1934) reporting on 100 childhood cancers found sarcomas most frequent (33 per cent). At the Birmingham Children's Hospital, England, no sarcomas of the soft tissues were reported by Smellie (1951). Lawrence and Donlan (1952) reporting from Indiana University listed 42 malignant tumors of the soft somatic tissues of a total of 370 malignant neoplasms in children under 15 years of age.

These data indicate that sarcomas of the soft tissues are a major form of cancer in childhood. The different incidences of this form of cancer reported from the different hospitals are undoubtedly the result of selective admissions in certain institutions.

The supporting organs of the body are thus the frequent seat of both benign and malignant tumors in children. Of the six tissues in juveniles most frequently afflicted by cancer (central nervous system, bone, eyes, genito-urinary system, blood and lymphoid system, and soft somatic tissues), neoplasms of the central nervous system, eye, kidney, and lymphomas have been the subjects of many reports in the literature. Sarcomas of the soft somatic tissues, however, have received only scant attention and most publications consist only of individual case reports.

TABLE II.—CAUSES OF DEATH IN NEW YORK CITY IN 1950

Disease	Age groups, years				
	0–4	5–9	10–14	11–19	All ages
Total (all causes)	4,452	273	196	373	79,082
Infections and parasitic disease	119	35	22	53	2,873
Tuberculosis (all forms)	61	10	7	36	2,321
Neoplasms	130	71	41	53	15,831
Allergic, endocrine system, metabolic, nutritional	11	5	3	2	1,919
Blood and blood-forming organs	10	4	1	5	163
Nervous system and sensory organs	63	18	13	13	5,686
Circulatory system	4	9	31	47	36,659
Respiratory system Pneumonia (all forms)	525 40	28 14	14 10	15 9	2,917 239
Digestive system	129	15	3	6	3,293
Genitourinary system	15	10	9	26	1,135
Bones and organs of movement	8	0	1	0	102
Certain diseases of early infancy Birth injury	2,521 369	0 0	0 0	0 0	2,521 369
Accidents, poisoning, and violence	196	66	47	104	4,521
Homicides	34	0	4	19	329

This presentation reviews the natural history and effects of treatment of 51 sarcomas of the soft somatic tissues in children, some treated by the Mixed Tumor Service of the Memorial Cancer Center and others by the Pack Medical Group. The group comprised 7.1 per cent of all patients (717) observed bearing soft somatic tissue sarcomas. Sarcomas may develop in any place where supporting tissue occurs. The soft somatic tissues are singled out in this report since it represents the bulk of the tissues of support and neoplasms occurring within them express most freely their growth patterns. This neoplastic category, therefore, represents a unified clinical entity which requires specific methods of treatment.

The histogenesis and nosology of sarcomas is presented in Chart I. The number of tissues which are derivatives of the primitive mesenchyme and from which the sarcomas

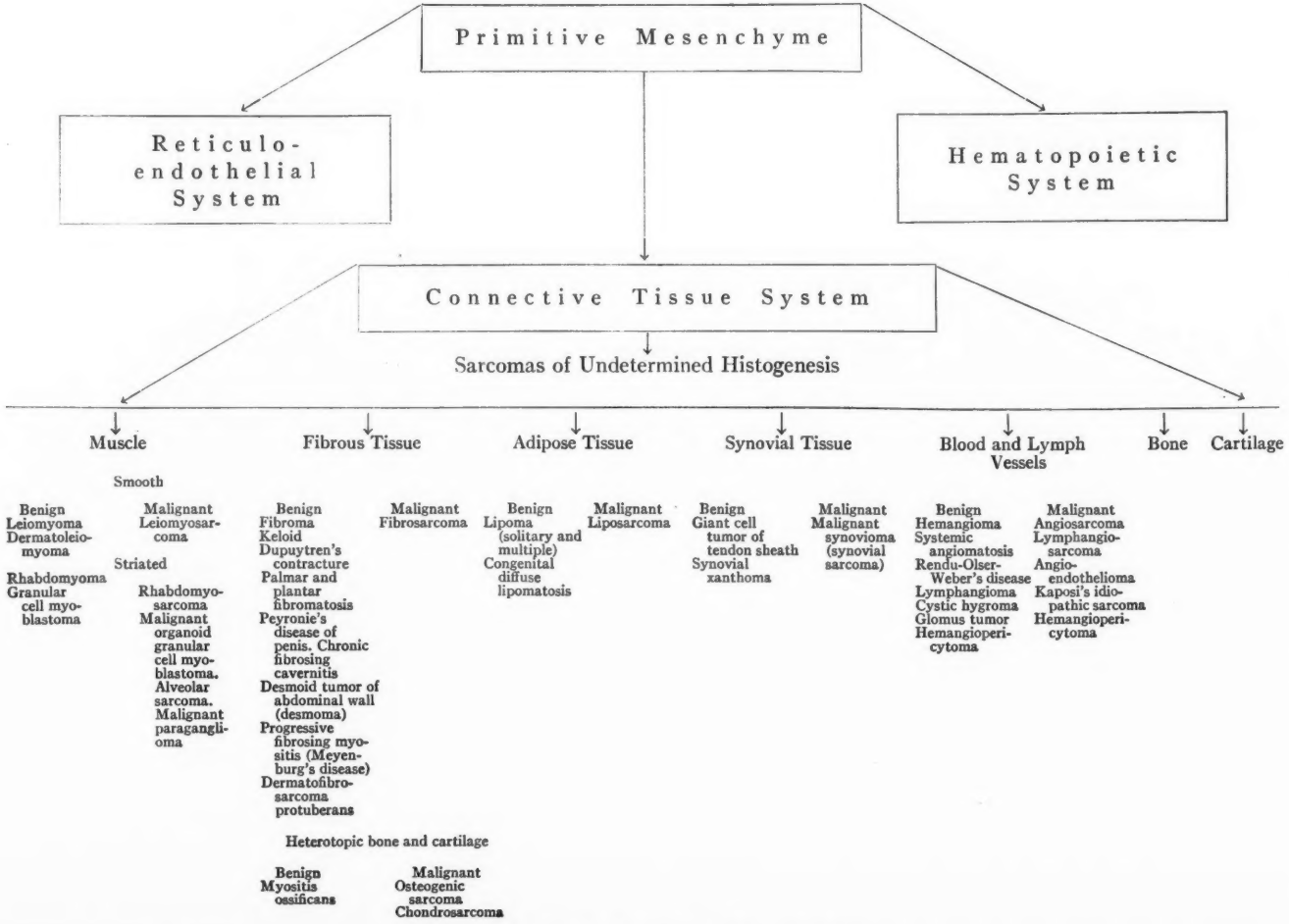

Chart 1. The nosology of tumors of soft somatic tissues.

under discussion arise is shown. This chart indicates why so frequently an intermingling of different structural components comprises a given neoplasm. Thus fibrous tissue structures are almost always present in synovial sarcomas, and an osteogenic sarcoma may form in regions of ectopic bone formation in soft somatic tissue. The chart further includes certain sarcomas in which the tissue of origin could not be identified and which are, therefore, labeled "sarcomas of undetermined histogenesis." In the total series there were 261 such unclassifiable sarcomas in all age groups, and of these 23 (8.1 per cent) were in children. Tissue culture studies by Murray and Stout have afforded a means of identifying characteristics which permit correct classification of certain undifferentiated sarcomas. However, because of the nature of mesenchyme and its derivatives and the great ease with which one tissue of this organ can transform to the structure of another tissue, such as osteogenesis occurring in soft somatic tissues, it is believed that in certain highly anaplastic sarcomas it is not possible by any method available at present absolutely to identify the tissue of origin. These tumors are best listed in the repository of sarcomas of undetermined histogenesis, and their end results and natural history are so analyzed. To do otherwise would obscure data for the specific neoplasm with which they are classified. This has occurred frequently when certain of the nonclassifiable sarcomas were labeled "fibrosarcoma." The end results obtained in treating *fibrosarcomas* were accordingly obscured.

TABLE III.—MALIGNANT TUMORS WHICH SEEM TO HAVE SIGNIFICANT RELATIONSHIP WITH AGE PERIODS

	Age		Most frequent tumors
Infancy	1–10 months "At first the infant, mewling and puking in the nurse's arms"	Birth to independent nutrition	Wilms', adenomyosarcoma of the kidney, ocular glioma
Childhood	10 months to 7th or 8th year	To development of senses	Ocular glioma, Wilms' tumor
Presexual	8th to 14th year "And then the whining schoolboy, with his satchel and shiny morning face, creeping like snail unwillingly to school"	Intermediate stage between childhood and adulthood	Usually free of malignant tumors
Pubertal	To 28th year (males) To 24th year (females) "And then the lover sighing like furnace, with a woeful ballad made to his Mistress' eyebrow"	From puberty to end of growth period	Endothelial, myelomas, thymomas, gliosarcomas, esticular, sarcoma
Maturity	"Then a soldier full of strange oaths, and bearded like the bard; And then the justice, in fair round belly with good capon lined"	From end of growth to sexual decline (males), menopause (females)	Great host of malignant tumors
Senescence	"Second childishness, and mere oblivion, sans teeth, sans eyes, sans taste, sans everything"	From menopause (females) and from sexual decline (males) to demise	Basal cell epithelioma of skin, squamous cell carcinoma of skin, lip, buccal mucosa, floor of mouth and vulva, carcinoma of prostate gland

The most frequent classified sarcoma noted in this series was the malignant neurilemmoma, and its occurrence in children under 15 years of age comprised 15.2 per cent of all patients bearing malignant neurilemmomas. Although as many liposarcomas were observed as were the malignant neurilemmomas, the number seen in children was only 6.7 per cent of all patients observed with liposarcoma. Fibrosarcomas and angiosarcomas comprise 10.2 and 10.5 per cent respectively of all patients bearing these tumors. The remainder of the sarcomas in children varied from 2.6 (1 patient with dermatofibrosarcoma protuberans) to 8.1 per cent of the total number of sarcomas (Table III). No instance of Kaposi's sarcoma was seen in children.

Of 24 sarcomas of the soft somatic tissues reported by Andersen from the Babies Hospital in New York, there were 5 fibromas, 3 rhabdomyosarcomas, 2 leiomyosarcomas, 1 embryonal lipoma of low malignancy, 1 malignant hemangiopericytoma, and 12 were unclassified sarcomas.

Table IV presents the incidence of sarcomas of infancy and childhood analyzed according to the histologic type of the tumor. The data evaluate the relationship of sarcomas which occur in children less than 15 years of age to the total incidence of soft somatic tissue neoplasms occurring in patients of all ages.

TABLE IV.—TUMORS OF SOFT SOMATIC TISSUES OF INFANCY AND CHILDHOOD (INCIDENCE ACCORDING TO HISTOLOGIC TYPE OF TUMOR)

Histologic type of tumor	Total No. cases	Patients 15 years of age and less	
		No.	Per cent
Total cases	717	51	7.1
Sarcoma of undetermined histogenesis	261	23	8.1
Liposarcoma	105	7	6.7
Rhabdomyosarcoma	100	4	4.0
Synovioma	60	3	5.0
Kaposi's sarcoma	48	0	0.0
Malignant neurilemmoma	46	7	15.2
Fibrosarcoma	39	4	10.3
Dermatofibrosarcoma protuberans	39	1	2.6
Angiosarcoma	19	2	10.5

GENERAL PRINCIPLES OF TREATING SARCOMAS OF THE SOFT SOMATIC TISSUES IN INFANCY AND CHILDHOOD

The broad aspects of treating the soft supporting tissue sarcomas will be discussed and the end results analyzed.

Attitude toward treatment of childhood cancer. The attitude toward the treatment of cancer in childhood has evolved through two distinct approaches. Most of the early literature inferred that no differences existed in the natural history of cancer in childhood and in the adult. As increased reports of malignant neoplasms of the very young became available, certain distinguishing characteristics between cancer in the younger individual and cancer in the older individual became apparent. For example, the ratio of sarcomas to carcinomas is much greater in children than in adults, certain organs are the host for cancers in children more frequently than in adults (eye, adrenal cortex, and testes). Certain embryonal tumors or teratomas may appear benign histologically but clinically are highly malignant while others, such as melanomas, in children are usually benign clinically although they may demonstrate a high degree of malignancy by histologic criteria. Malignant tumors, as a rule, do seem to grow more readily in the very young without evoking a protective objection by the host.

The characteristics of rapid growth with a tendency to early metastases by many malignant neoplasms in children were responsible for the second attitude regarding the philosophy of treating childhood cancer, namely, one of abject pessimism. This pessimistic attitude permeated the profession so that certain physicians refrained from giving any form of treatment, and it infiltrated to the parents who would not bring the child with a tumor to the physician, feeling that the situation was hopeless.

The end results in the treatment of sarcomas in the soft somatic tissues of children of this series and reports from other clinics on the end results in the treatment of cancer in children should dispel the pessimistic attitude pertaining to this important subject. It should encourage every effort to treat each case of childhood cancer, because cures can be obtained. We are entering a third era, that of hopeful endeavor to establish early diagnosis and institute adequate treatment in children.

The end results in the treatment of all sarcomas of the soft somatic tissues in infancy and childhood reveal that of the 51 children treated 16 are living apparently without recurrence 5 years and more after treatment. The 5 year cure rate of all determinate cases treated for sarcoma of the soft somatic tissues is 42.1 per cent (Table V). Twenty-three of the 51 have died as the result of the sarcoma and 4 are listed in the indeterminate group having been lost to follow-up examination.

Table VI reveals the curability of all sarcomas in relation to the location of the tumor.

TABLE V.—TUMORS OF THE SOFT SOMATIC TISSUES OF INFANCY AND CHILDHOOD, 5 YEAR END RESULTS

	No.	
Total cases		51
Indeterminate cases (refusing treatment, not completing treatment and lost track of, or treated elsewhere)		4
Determinate cases (entire series)		47
Treated within past 5 years	8	
Treated over 5 years ago, used for evaluating 5 year cures	39	
Failures (died of the sarcoma)	23	
Successful results (living without evidence of sarcoma 5 years or more)	16	
Cures: 5–9 years	6	
10–15 years	4	
15 years or over	6	
Survival rate	42.1	per cent

The overall mortality equaled 43.1 per cent of the determinate cases. The highest mortality occurred in patients who bore sarcomas of the lower extremity, shoulder, and torso, and ranged from 44.4 to 66.6 per cent. Patients with sarcoma of the hand apparently enjoyed the best prognosis (none died as the result of the sarcoma) as did those of sarcoma of the arm (66.6 per cent, 5 year cure rate of the determinate cases).

Analysis of the end results in relation to the age of the patient reveals that the best prognosis apparently was enjoyed by the 9 patients under 1 year of age (Table VII). Only 1 of these 9 succumbed from the sarcoma. Three are alive and free of evidence less than 5 years after treatment, and an additional 3 are alive and free of evidence 5 years or longer after treatment. Two are classified as indeterminate because they were lost to follow-up. The mortality rate for the patients between 6 and 10 years of age is 60 per cent; in the group between 11 and 15 years of age the mortality is 41.6 per cent. From these data it would appear that the best results can be obtained when the sarcomas are treated in younger subjects. These results should indicate further that malignant neoplasms occurring shortly after birth do not represent an incurable end result of a prenatal disturbance.

Analysis of the end results of the entire group of children bearing sarcoma of the soft somatic tissues analyzed according to the type of treatment reveals some rather interesting indices (Table VIII). There were 11 patients treated by excision alone; 5 are apparently free of evidence less than 5 years and 3 are free of evidence 5 years or more. The mortality rate in this group is 9.1 per cent. Of those treated by excision plus postoperative irradiation 4 of the 7 so treated are alive and well 5 years and longer after treatment. There were 24 patients treated by irradiation alone and of this group 11 were given irradiation only for palliative purposes. Eight additional patients treated by irradiation are alive and apparently free of disease over 5 years after treatment. There were 2 patients treated by amputation and one is well over 5 years and the other is dead. Two patients were treated by intrascapulothoracic amputation and they are both well but the elapsed time is less than 5 years, so final evaluation must await further follow-up. One patient who was treated by hip joint disarticulation died, and another was unsuccessfully treated by hemipelvectomy.

TABLE VI.—TUMORS OF SOFT SOMATIC TISSUES OF INFANCY AND CHILDHOOD END RESULTS IN RELATION TO LOCATION OF TUMOR

Location of tumor	Total cases No.	Living without sarcoma		Died with sarcoma		Indeterminate cases No.
		Under 5 years No.	5 years and over No.	No.	Per cent	
Total cases	51	8	16	22	43.1	5
Hand	2	0	1	0	0	1
Arm	13	6	4	2	15.3	1
Shoulder	3	0	1	2	66.6	0
Leg	7	1	1	4	57.1	1
Thigh	9	0	4	4	44.4	1
Back, chest wall, and abdominal wall	17	1	5	10	58.8	1

These data in no way reflect the efficacy of a given modality for curing sarcoma because the more radical measures were utilized for the more extensive neoplasms.

These data do demonstrate that cures can be obtained. Continued critical evaluation will determine the proper combination of treatment methods that should be applied to a given child with a sarcoma of the soft somatic tissues.

SOFT TISSUE SARCOMAS IN CHILDREN ANALYZED ACCORDING TO HISTOLOGIC TYPE

The 5 year "cure" rates following treatment of soft somatic tissue sarcomas are presented in Table V.

The overall 5 year "cure" rate for the 38 determinate infants and children is 42.1 per cent which is slightly better than 39.2 per cent of the overall series of 418 determinate patients of all ages with sarcomas. Thus, sarcomas of supporting structures in infants and children can be treated as successfully, if not more so, than their congeners in the adult. The specific sarcoma which reacted most satisfactorily to treatment was the malignant synovioma with a survival rate of 66.7 per cent. This value is in sharp contrast

TABLE VII.—TUMORS OF SOFT SOMATIC TISSUES OF INFANCY AND CHILDHOOD END RESULTS IN RELATION TO AGE OF PATIENT

Age of patient, years	Total cases No.	Living without sarcoma		Died with sarcoma		Indeterminate cases No.
		Under 5 years No.	5 years and over No.	No.	Per cent	
Total No. cases	51	8	16	22	43.1	5
Under 1	9	3	3	1	11.1	2
1–5	20	1	8	10	50.0	1
6–10	10	1	2	6	60.0	1
11–15	12	3	3	5	41.6	1

to the 5 year survival of 21.6 per cent of patients of all ages bearing synovial sarcomas. Children with liposarcoma revealed a 57.1 per cent 5 year survival and those with rhabdomyosarcoma and fibrosarcoma each enjoyed a 50 per cent 5 year "cure" rate.

Young patients with sarcomas of undetermined histogenesis—usually a malignant variety of tumors—showed a 35.2 per cent 5 year survival. Patients with malignant neurilemmoma had a 28.6 per cent survival rate and the 1 child with angiosarcoma succumbed from the tumor. Chart 2 reveals the total experience of patients of all ages bearing soft somatic tissue sarcomas compared with that of the juvenescent human under 15 years of age. It may be noted that the end results in the infants and children compare favorably with the overall prognoses.

In certain groups a betterment of results is noted in sarcomas of childhood (synoviomas 66.7 per cent in children versus 21.6 per cent survival rate for adults). In no group was the end result in the lower age brackets significantly poorer than in adults.

TABLE VIII.—TUMORS OF SOFT SOMATIC TISSUES OF INFANCY AND CHILDHOOD END RESULTS IN RELATION TO TYPE OF TREATMENT

Type of treatment	Total cases No.	Living without sarcoma		Died with sarcoma		Indeterminate cases No.
		Under 5 years No.	5 years and over No.	No.	Per cent	
Total cases	51	8	16	22	43.1	5
Excision only	11	5*	3	1*	9.1	2
Excision and irradiation	7	0	4	3*	42.8	0
Irradiation only	24	1	8	14†	58.3	1
Amputation	2	0	1	1	50.0	0
Interscapulothoracic amputation	2	2	0	0	0	0
Hip joint disarticulation	1	0	0	1	100.0	0
Hemipelvectomy	1	0	0	1	100.0	0
No treatment	3	0	0	1	33.3	2

*In one case treatment was given for palliative purposes only.
†In 11 cases treatment was given for palliative purposes only.

DISCUSSION

Sarcomas of the soft somatic tissues of infants and children represent a histologic and clinical entity which, although not common, represents, nevertheless, one of the major forms of cancer of the developing infant and child. The presence of a malignant neoplasm in a newborn infant offers material for great speculation concerning etiology and pathogenesis. The carcinogen must be potent for it has a short period to exert its influence (maximum of 9 months). Willis has indicated that the genesis of teratomas of infants must be related to the chemistry of the "organizers" or growth hormones which determine the orderly developmental patterns and that the locations of teratomas suggest growth disturbances from the primary axis—the notochord and contiguous structures—which is derived by invagination at Hensen's node in the early embryo and which constitutes the primary organizer. He indicates that blastulas deprived of their primary organizer regions can grow and differentiate into a variety of tissues but do so in a chaotic manner and without forming an axis or defined organs. He suggests that teratomas may represent clusters of tissue which early escaped the action of the primary organizer.

Localized chemical aberrations within the embryo could be responsible for the formation of sarcomas of the soft somatic tissues. Sometimes maternal influences will produce localized effects, for example, rubella in the mother frequently produces cataracts in the human offspring. It has been shown in animals that insulin given to the parent results in congenital deformities, possibly by altering intrauterine environment (Lawrence).

Certain postnatal reactions of fibrous tissue give leads of prenatal influences which may be factors for sarcomatous formations. The reaction of fibroblasts to testicular extract represents a recapitulation of their normal developmental history with acceleration of maturation and suggests that in normal development, aging, and repair there is a progressive series of changes with a shift from the amorphous to the fibrous elements of the intercellular substance.

The exact source of the intercellular substance is not known. It is most probably formed by the fibroblasts with a reciprocal relationship existing between the ability of the fibroblasts to produce collagen and the state of the surrounding media (changes in *p*H and temperature). Some investigators such as Nageotte believe that the intercellular substance is not produced by the fibroblasts but instead is manufactured by the body fluids.

It is of interest that in the so-called diseases of collagen an abnormality in the composition of the ground substance is present in addition to defects in the fibrous tissue. These findings suggest that a sufficient amount of normal ground substance must be available for the formation of normal fibrous tissue and that abnormal fibrous tissue may be due to abnormalities of ground substance from which the fibers are produced.

Stewart has demonstrated that fibroblasts in tissue culture become malignant when 20-methylcholanthrene is added to the culture media, and when these altered fibroblasts are injected into animals sarcoma demonstrating all the manifestations of malignancy will develop at the site of the transplantation. Nettleship has studied the sequence of events after the injection of 20-methylcholanthrene into hamsters. Within 24 hours after injection, marked edema of the connective tissue develops and certain connective tissue cells are found detached from the others and are swollen and granular. These cells, altered within 24 hours after injection of the carcinogen, develop into frank sarcoma in a smooth, gradual manner during a brief period. The altered cells proliferate and are present in groups, then large sheets of them are noted,

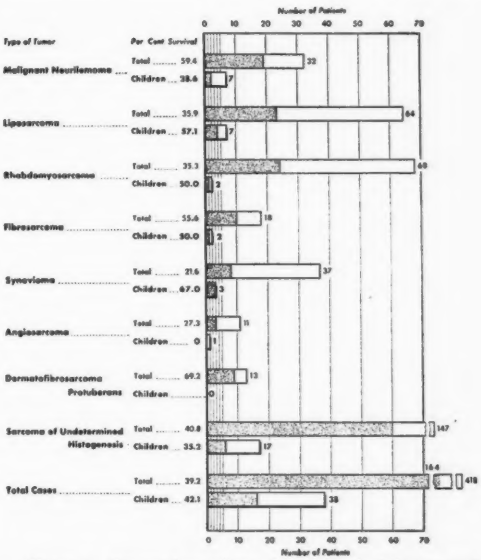

Chart 2. Comparison of survival rates in infancy and childhood with total survivals in patients with malignant tumors of soft somatic tissues.

and finally a sarcoma develops. These animal experiments suggest the possibility that alterations in the fluid media which bathes these cellular components of the fibrous tissue network may possibly play a role in inducing sarcomas in humans.

The nature of the alterations is dependent upon many factors including specie, race, familial factors, and even individual variations. The following is an example of specie alteration. If 20-methylcholanthrene is injected into guinea pigs, 20 per cent of the animals develop liposarcomas, but if the same chemical is injected into mice, none develops liposarcoma.

Selective senility. The reason for the differences in the behavior of cancer in the very young from that in older individuals is not understood. Certain cancers can well be explained on the basis of Cohnheim's theory of misplaced cell rests. Another important factor is the difference between the anatomic and physiologic ages of different structures within the organism during a given age of the individual. Thus, at the time of birth certain organs may be considered aged and commence

toward their involutional state, such as the thymus. Other structures may be mature as a result of the influence of maternal hormones, such as the vaginal epithelium, and others may lie dormant awaiting their selective stimuli to maturate, e.g., the breast. Due to certain inborn errors of metabolism a speeding up of the aging process occurs for either certain structures, such as the epidermis in xeroderma pigmentosa, or for the entire organism as seen in the Ehlers-Danlos syndrome. An example of senility at birth is seen in the placenta. Its calcareous, fibrotic, atrophic, and vascular changes are characteristic of old age. The placenta has the shortest life of any human organ, yet at times it is subject to the development of cancer (chorionepithelioma). This cancer formation is in keeping with its anatomic age.

The more frequent occurrence of sarcomas in infants and children than in adults is not completely understood. Chronic irritation has been demonstrated to produce certain sarcomas, as sarcoma in a burn scar. Whether irritating factors excite neoplastic formation during prenatal life is not known.

As the individual becomes older and as a result of the normal metabolic wear and tear of an organism, compounded by such stimuli for fibrous propagation from infection, trauma, or other noxious stimuli, it would seem that a richer soil for sarcomatous formation exists in the adult than in the child, but this situation does not prevail as sarcomas occur more frequently in children than do neoplasms of epithelial structures.

It is beyond the scope of this discussion to pursue this fascinating line of thought further, but the evidence is presented to indicate that prenatal influences can affect a localized segment of tissue with resultant formation of a sarcoma, entirely localized. Contrary to certain opinions, it does not reflect a generalized abnormality of the supporting structures of the organism and is thus akin to most sarcomas in the adult.

The stimulus for certain neoplasms is transmitted from parent to offspring via the genes and adheres to genetic laws, e.g., retinoblastoma, hereditary cartilaginous exostosis, familial polyposis of the colon, and multiple neurofibromatosis and lipomatosis as well.

In most sarcomas of the soft somatic tissues, however, either a limited portion of tissue has undergone sarcomatous transformation, as in rhabdomyosarcoma, or a larger segment of tissue may be doomed to sarcomatous formation which occurs at variable postnatal periods, e.g., neurilemmoma invading an entire major nerve trunk from its point of emergence from the spinal tract to its fibrillar ramifications.

Such ontogenetic background aids in formulating principles for treating sarcomas of the soft somatic tissues in the infant and child. It forces the physician to seek out the presence of certain neoplasms if a parent had suffered its presence (example: retinoblastoma); it offers the surgeon criteria for extirpating organs which are the seat of certain premalignant tumefactions (familial colonic polyps); and it routes the surgeon on his course for boldly treating localized sarcomas of the soft tissues in infants and children. The knowledge that they represent localized and at times limited tissue aberrations and not generalized structural dysfunction permits the surgeon to strive for complete eradication of neoplasm and its bed.

Infants and children tolerate radical operative procedures remarkably well, hence none should be deprived the benefits of a curative surgical attempt. So-called inoperability because of "frailty of the infant" usually reflects a frailty of the surgeon.

Analysis of the 51 sarcomas of the soft somatic tissues of this series, moreover, reveals that not infrequently a histologically malignant neoplasm will manifest a rather benign clinical course and be subject to cure, whereas in the adult the prognosis would more frequently be fatal. In addition, certain tumors in infants and children considered radioresistant on histologic criteria will respond dramatically to irradiation. Certain sarcomas in children have been described as reverting to a benign status either spontaneously or following irradiation, e.g., neuroblastoma reverting to a ganglioneuroma.

The observation that most sarcomas of the soft somatic tissues in children represent a

localized growth originating usually in a single nidus, combined with the fact that 42.1 per cent of all children bearing sarcomas of the soft somatic tissues treated by the authors have survived 5 years and longer are hopeful signs. It is the distinct impression of the authors that many of the children who delayed long periods or were inadequately treated before referral here could have been cured if adequate treatment had been given with dispatch.

The natural history of the specific sarcomas of this group offer signs for developing the surgical attack upon a given patient. Thus in patients bearing synovial sarcomas and rhabdomyosarcomas, because of the high incidence of metastases to lymph nodes, every surgical approach should consider resection of the regional lymph nodes. Metastases to lymph nodes have been described for every form of sarcoma. This is contrary to a common but mistaken impression that they metastasize only by way of the blood stream, and it should make the surgeon always consider the possibility of excising en bloc the regional lymph nodes which drain that anatomic segment in which the tumor has occurred. This consideration need not be great in such sarcomas as fibrosarcoma or liposarcoma where metastases to lymph nodes are rare. Because of the possibility of metastases to lymph nodes the nodes should certainly be excised, especially if the location renders itself suitable to an excision in continuity.

Other gross characteristics of the different sarcomas must be given consideration for the extent and type of operation to be performed. For rhabdomyosarcomas an entire muscle group should be excised if the decision is to treat it by wide local excision. In malignant neurilemmomas it is of interest that, despite extension along the intraneural and perineural lymphatics, metastases to regional lymph nodes are extremely rare. In certain instances it is essential to realize that an entire major nerve trunk is condemned to neoplastic formation, and in such instances the entire nerve must be resected, from the spinal column to the small filaments in the distal part of the extremity. It becomes necessary to perform an interscapulothoracic amputation with excision of the nerves as they emerge from the spinal canal, or perform a hip joint disarticulation or possibly a hemipelvectomy for malignant neurilemmoma of the lower extremities. This was done in 1 of our patients but despite the most radical type of surgical resection the neoplastic recurrence occurred in the lumbar plexus proximal to the point of resection. The characteristics of malignant angiosarcomas and rhabdomyosarcomas with their large number of thin-walled blood vessels and the frank bleeding which occurs readily following the least traumatization dictate that the normal tissue investiture should remain inviolate during the resection and that the gentlest of surgical manipulation be maintained. In view of the presence of venous tumor emboli occurring in such instances, it has been Booher's policy to ligate the femoral or axillary veins preparatory to the performance of the tumor resection. Most of the sarcomas of this group do not readily infiltrate contiguous structures but tend more to creep through tissue spaces entering into every tissue crevice which does not offer much resistance to its propagation. This feature more or less will give the surgeon a sense of security when observing normal muscle and other tissues in the vicinity of the tumor, not realizing that the neoplasm has extended through the tissue spaces. It is only after the tumor has grown to great proportions that it will readily invade the contiguous structures. Because of this growth characteristic, it is essential that the surgeon resect very widely, particularly in regions of much loose areolar tissue.

When sarcomas occur in regions of bulky soft tissues the tendency is to extend centripetally and to grow in more or less an expansile manner. In such instances, appreciating the mode of local extension, wide areas of contiguous structures can be removed, these to include all other tissue within the confines of the sarcoma. It is futile to attempt to dissect out nerves or blood vessels which traverse the neoplasm, for such attempts will vitiate the chance for cure. Contrariwise, when the neoplasms occur in condensed tissues, such as hands and feet,

or in the vicinity of joints where numerous tendons converge, the sarcoma will infiltrate intimately all these structures and will invade them. In such cases it is necessary in almost all instances to amputate the involved member in order to obtain a cure. It is not possible to set forth didactic criteria for the extent of resection in any patients bearing sarcomas of the soft somatic tissues as each case must be individualized according to the background and natural history of the specific sarcoma. The therapeutic approaches will vary from a wide surgical excision to the most radical amputation. Irradiation for the most part should not be utilized as the sole method of treating sarcomas. If the decision is to treat the patient by wide local surgical excision and postoperative irradiation, the fact that irradiation will be administered after operation should in no way deter the surgeon from effecting the most radical surgical procedure necessary. Utilization of an inferior therapeutic modality—irradiation—as a crutch for the inadequate application of the superior surgical method of ablating these neoplasms is to be condemned.

Because of the pseudohumane and sentimental considerations which every surgeon must suffer in deciding on a radical extirpation of sarcomas in infants and children, many have yielded to their emotional impulses and have performed a limited and conservative excision to avoid surgically mutilating the infant or child. We heartily agree to limited excision where indicated, but only by a complete understanding of the behavior patterns of each of the tumors of children can one decide when the excision can be conservative or when it must be radical. In those instances in which only the most radical type of surgical resection will offer hope of ablating the cancer, fear of mutilation and thoughts of reconstruction must be secondary to the extensive excision necessary to cure the patient. Failure to do this will doom the patient or will necessitate repeated resections with the eventual result that a more radical procedure may be necessary for the treatment of recurrences than would have been indicated for the treatment of the primary neoplasm. The surgeon can for the most part be most conservative by being radical at the onset.

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TREATMENT OF ATRESIA OF THE ESOPHAGUS BY THE TRANSPLEURAL APPROACH

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THE problem of esophageal atresia with or without tracheoesophageal fistula has been a difficult one to handle for many years. The first case of successful management was recorded in medical literature by Ladd only a decade ago. Sixty-one cases have been seen at the Children's Hospital of Philadelphia since 1947 and it was thought that a review of the cases was indicated, especially since we believe that there have been advances made following the institution of a routine transpleural operative approach in 1950. Prior to that year, the classical, retropleural procedure had been used and the results were so discouraging that it was decided to operate transpleurally. This report records the experience of the authors with both retropleural and transpleural procedures during the period 1947 through 1952.

HISTORICAL BACKGROUND

Before 1929, the operative correction of this lesion consisted of a gastrostomy. The mortality remained 100 per cent, due to aspiration pneumonia. Some then tried to re-establish esophageal continuity by a multiple stage procedure in which the fistula was closed and the proximal blind stump brought out in the neck —all by extrapleural technique. A gastrostomy was combined with this, and subsequent stages consisted of fashioning antethoracic skin tubes to connect the cervical esophagus and the stomach. The discouragement and failure of these attempts were recorded by Lanman in 1940. However, in the course of such experiences several primary end-to-end anastomoses were attempted, and, while unsuccessful, they pointed the way to the desirability of this method. Ladd and Leven almost simultaneously performed the first successful multiple stage operations on the tracheoesophageal problem in 1939. However, it remained for Haight (3) in 1941 to fulfill the expectations of many that a successful end-to-end anastomosis would eventually be accomplished. Since then, the majority of operators in the field have been using this way of handling the anomaly, reserving the ingenious methods of Sweet, Longmire, and Potts for those fortunately few cases in which the distance between proximal and distal esophageal segments is too great for primary anastomosis. Almost uniformly the incisional approach to the primary union has been posterior and extrapleural.

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CLINICAL PICTURE

The clinical picture of esophageal atresia has been well described by other authors. The diagnosis of atresia of the esophagus, with or without tracheoesophageal fistula, should be suspected when a baby is born cyanotic and, after the aspiration of viscid mucus from his nasopharynx, becomes cyanotic again with the reaccumulation of nasopharyngeal secretions. The diagnosis should not be delayed after the first feeding when with the second swallow the feeding is forcibly ejected through the nose and mouth. Unfortunately, most diagnoses are delayed beyond this time and aspiration pneumonia, which is one of the major complications of this anomaly, becomes well established.

The diagnosis of atresia of the esophagus can be confirmed by the passing of a soft rubber catheter through the nose into the upper esophagus. When atresia exists, an obstruction will be met just below the clavicle, approximately 9 to 11 centimeters from the nose. Roentgenograms may be taken for visual confirmatory evidence, with or without a contrast medium. We prefer to use no medium, but certainly a radiopaque oil is prefer-

TABLE I.—MORTALITY STATISTICS

	Living	Dead	Mortality Per cent
Ladd	11	23	68
Boston Children's (2)	109	115	51
Haight (4)	41	45	52
Potts	15	17	53
Arnheim	3	16	84
Leven	56	40	42
Koop and Kiesewetter	27	34	56

able to barium because of the probability of aspiration. Air in the gastrointestinal tract denotes the presence of a fistula between the lower esophagus and the tracheobronchial tree.

TECHNIQUE

The transpleural approach to esophageal atresias is not original with the authors. It has been used by others in occasional cases, and has been advocated in the literature by Singleton and later by Lyon. However, as far as can be ascertained, this is the first large group of patients treated by this method. We had confidence in starting a series because of the wide experience gained by our anesthetists with endotracheal anesthesia, during which remarkably few respiratory complications arose.

The infant, under endotracheal anesthesia, is placed in the left lateral decubitus position and an incision made from the costochondral junction back to the sacrospinalis muscle. The pleural cavity is entered through the third or fourth interspace, and adequate exposure is gained by using a self-retaining retractor without dividing any ribs. The lung is retracted to expose the azygous vein which is divided. A small No. 8 French catheter is then inserted via the nares into the esophagus by the anesthetist to facilitate identification of the upper pouch. The mediastinal pleura is opened and the upper portion of the esophagus is mobilized as far cephalad as possible for future anastomosis. The lower esophagus and fistula are then identified posterior to the trachea and medial to the prominent vagus nerve. Most fistulas enter the tracheobronchial tree near the carina or just below it in the right main bronchus. The dissection of the lower esophagus must be gentle because it lacks both the blood supply and the muscular hypertrophy found in the proximal segment. The dissection of the lower esophagus has had to be carried down to the diaphragm in a few cases and has been followed by successful anastomosis. The separation of the esophagus from the trachea is done by placing a strip of rubber drain around the esophagus for traction, dividing the fistula and oversewing the tracheal side a short distance at a time with 5-0 silk. After completing the division of the fistula, a running stitch reinforces the first suture line. The closure is then tested under water for air leaks.

The esophageal anastomosis is a one layer closure of simple stitches using 5-0 silk. It is important to trim any ragged edges on the lower esophagus before carrying out the anastomosis. Four guide sutures are placed around the circumference of the lower segment for traction and exposure of the lumen. The upper segment must be opened at its most dependent portion, and it is usually wise to cut an actual section out of the atretic portion rather than to make a mere slit, in order to minimize the obstruction when the two disproportionate segments are anastomosed.

The mucosa must be caught with each stitch as the closure is carried out. With one-third of the circumference secure, the No. 8 French catheter lying in the proximal segment is passed through the anastomosis to facilitate the remaining two-thirds of the closure. As few as 9 stitches have been used although 12 is an average number. If the anastomosis is not under great tension and is tight, the mediastinal pleura is reapproximated and the chest closed without drainage. If the anastomosis has sufficient tension on it so that one would hesitate to feed across it early, a small diameter polyethylene tube with a rubber catheter tip is threaded down into the stomach under direct vision. If the presence of this tube in any way exerts pressure on the anastomosis, it is withdrawn and a gastrostomy is performed then or within 48 hours as a separate procedure under local anesthesia.

Postoperative care includes an atmosphere of high humidity, frequent nasopharyngeal aspirations of mucus, liberal use of antibiotics,

and parenteral fluids without salt in quantities less than used for most other neonatal conditions. The anesthetists do direct tracheal aspirations daily for several days as indicated, and either blood or plasma is given supportively each day.

Feedings by mouth, gastrostomy, or tube are begun on an average of 48 to 72 hours after operation, although some children have been fed as early as 24 hours postoperatively.

RESULTS

In the 6 year period, 1947 to 1952, sixty-three patients have been admitted to the Children's Hospital of Philadelphia with a diagnosis of esophageal atresia, with or without tracheoesophageal fistula. Sixty-one were operated upon (9 by resident house staff) and will comprise the material for this analysis. The remaining 2 died before surgery could be carried out. Wherever possible and desirable the results will be analyzed by breaking them down into two groups—those operated upon by the retropleural technique and those done by the transpleural technique.

Mortality. When the retropleural technique was used, 14 of 19 patients died, a mortality of 73.7 per cent. Twenty of 42 patients operated upon transpleurally died, a mortality of 47.6[1] per cent. The overall mortality for the entire group was 55.7 per cent. There were no deaths on the operating table.

These figures are compared with other large series reported in Table I. If we had reported our first 15 transpleural cases we could have cited a mortality of only 26 per cent.

Mortality alone, in a defect such as atresia of the esophagus, is not the sole criterion of the worth of a given technique.

Color. There seems to be no sex predominance in this series of 31 females and 30 males, but it is of interest to record an apparent predilection for the white race. Although our admission ratio of white and colored patients is about 3 white for each colored child, only 2 cases here reported were in colored infants.

Age at operation. The age of the patient at the time of operation bears a definite relationship to his chances for survival, and is summarized as follows: Of the 41 infants operated upon before they were 72 hours old 22 survived, 19 died, a mortality of 46 per cent. Of the 20 operated upon after they were 72 hours old 5 survived, 15 died, a mortality of 75 per cent. Twenty-two of the 27 patients now alive (82 per cent) were operated upon before they were 72 hours old. The youngest survivor was 16 hours old and the oldest 9 days.

Weight. The mortality in this series is inversely proportional to the weight of the infant. The highest mortality is in the premature group; 17 of our patients were under 5 pounds, with a distressing mortality of 82 per cent. There were 42 over 5 pounds, with a mortality of 43 per cent. The admission weights of 2 were not recorded. The smallest infant was 3 pounds 2 ounces, and the largest was 7 pounds 5 ounces. The lightest survivor weighed 4 pounds 8 ounces, and the heaviest child now living was 7 pounds 4 ounces.

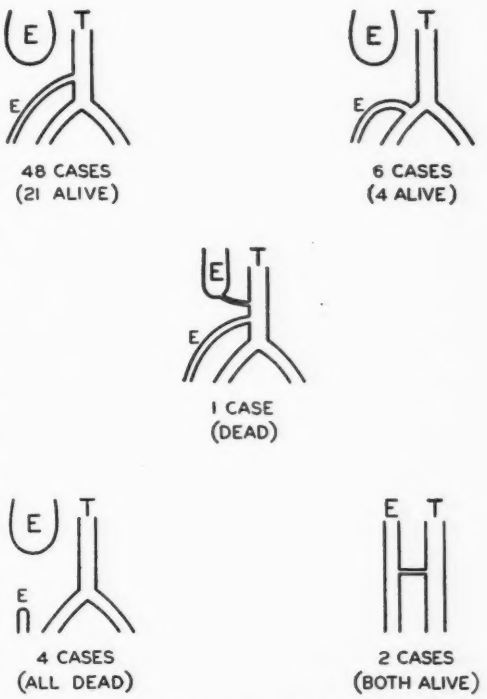

Fig. 1. Anatomic types of atresia of the esophagus.

[1]Since this study was undertaken, 11 additional cases have been operated on transpleurally with 7 survivals. This would make the mortality in all the transpleural cases 45.4 per cent.

X-ray examination. An attempt was made to determine whether the use of radiopaque material in the diagnosis of this condition played any appreciable part in the mortality. In 30 cases it was used and in 31 it was not. The mortality in the two groups was essentially the same.

All patients who had preoperative films were analyzed with respect to the influence of preoperative pneumonia or atelectasis on mortality. Thirty-one cases were diagnosed by roentgenologists as having pneumonia or atelectasis. The mortality in these patients was essentially the same as in those with roentgenologically clear lung fields.

Anatomic types (Fig. 1). Forty-eight patients had the common anomaly of atresia of the esophagus with a fistula between the distal esophagus and the trachea. Twenty-one of these are now alive. Six infants had atresia with a fistula connecting the distal esophagus and the right main bronchus; 4 of them survived. In only 1 patient was there a fistula between the proximal esophagus and the trachea. This infant had massive pulmonary atelectasis probably on the basis of amniotic aspiration in utero, and it died. Two patients had a fistula without atresia and are alive. Four infants had atresia without fistulas and all are dead; 3 of these had no distal esophagus.

Associated congenital anomalies. Major congenital defects were noted in 16 of the 61 patients. In several patients the lesions were multiple, there being 22 anomalies in 16 patients: congenital heart disease in 6 cases, atresia of bile ducts in 1, abnormalities of urinary tract in 4, mongolism in 2, harelip and cleft palate in 1, imperforate anus in 3, absence of arm in 1, reduplication of esophagus in 1, bowel atresia in 1, absence of tracheal ring in 1, and omphalomesenteric cyst in 1 case. Minor defects, such as hemangiomas, are not considered.

In addition to these associated anomalies, 3 patients had complications in their management. One had a severe erythroblastosis and 2, who did not survive, had pyloric stenosis. The clinical course of the latter 2 did not suggest the diagnosis even in retrospect.

Several of the associated lesions were in themselves incompatible with life. It is our belief that 5 patients in the retropleural group and 3 in the transpleural series would have survived had they not had these severe multiple anomalies.

Operative procedures. In the 57 cases in which there was a distal esophagus, an attempt was made to do a primary end-to-end anastomosis after closure of the fistula. This was accomplished in all but 1 case in which a cervical esophagostomy was carried out after closing the fistula and the distal esophagus. This child awaits definitive surgery.

In the group of 19 patients who were operated upon by the retropleural approach, 6 had gastrostomies for feeding purposes and 2 for retrograde esophageal dilatations. In the transpleural group of 42 patients, 6 gastrostomies were done for feedings, 2 for dilatations. A polyethylene tube was employed 9 times across the anastomosis in the transpleural group.

The operating time in the transpleural group was considerably reduced, which we believe is of significance in the mortality. The average retropleural operating time was 2 hours and 4 minutes, while in the transpleural group the average time was 1 hour and 40 minutes. The shortest "skin to skin" operation in the transpleural group was 45 minutes, and 4 operations were performed in less than an hour.

Complications. Serious complications encountered in the surgery of esophageal atresia have been of three types:

1. Respiratory obstruction.—In our experience no infant patients have more aberrations in respiratory physiology than do those with postoperative atresia of the esophagus. Constant nursing care, frequent mucus aspirations, and a house staff prepared to meet emergencies overcome most of the difficulties.

In this series, tracheotomies were done 4 times, none we believe because of endotracheal anesthesia. One infant in the retropleural group had no tracheal rings; this child lived. In the transpleural group 3 tracheotomies were necessary. Two were performed to obtain adequate airways; in 1 of these cases bronchoscopy had been done elsewhere before admission. One tracheotomy was carried out 40 days postoperatively for a tracheobronchial

infection. This case was the only death among the tracheotomies.

2. Esophageal stenosis.—Six patients required dilatation of the anastomosis, 2 in the retropleural and 4 in the transpleural group. Of the 6, 4 had gastrostomies for retrograde bouginage. All are alive and well.

3. Leaking anastomoses.—Six anastomoses leaked, 1 of which was in the retropleural group. The 5 patients in the transpleural group were operated upon a second time without success.

Air leaks at the site of fistula closure have not been experienced, and only 1 closure has compromised the lumen of the trachea and produced symptoms.

Follow-up. Follow-up data are available on 23 of the 27 surviving members of our series, brought up to date as of February 1, 1953 by personal examination or mail report. Of the 23 followed, 20 are asymptomatic and developing normally. One still has a tracheotomy at the age of 1 year, 1 has a gastrostomy and is undergoing esophageal dilatations, and 1 has a cervical esophagostomy and gastrostomy and will need further definitive surgery.

DISCUSSION

Early diagnosis is of paramount importance in the successful management of this and other surgical lesions of the newborn. In 82 per cent of our patients now alive, diagnosis was made and operation performed before they were 72 hours old. Only 38 cases of the whole group were diagnosed before the infant was 72 hours of age, which gives a survival among the early cases of 58 per cent. By contrast, only 5 of the remaining 23 patients are alive, giving a survival of only 22 per cent, when diagnosis of the lesion was delayed beyond the first 3 days of life.

It is apparent that esophageal atresia is more prevalent in premature and small babies. Which is cause and which is effect cannot be accurately assessed, but 90 per cent of the patients in this series were below 7 pounds. Thirty-eight per cent of cases occurred in premature infants (under 5½ pounds).

The greatest therapeutic challenge was presented by the 4 patients with no distal esophagus, or a segment not long enough to anastomose to the proximal pouch. Three of these had other anomalies or situations which could be considered incompatible with life so that the mortality is a reflection of more than the lesion under discussion.

The use of the transpleural approach to atresia of the esophagus was not the only change in managing these patients as compared with the retropleural route. Fewer sutures were used in the anastomosis, gastrostomies were avoided where possible, and feedings were begun by mouth as early as seemed safe. This combination seemed to prevent the narrowing of the esophageal lumen at the site of the anastomosis, and postoperative dilatations were not troublesome.

Diagnosis of a tracheoesophageal fistula without an accompanying atresia is difficult. One of the 2 reported here was seen by the bronchoscopist on the third attempt at visualization after repeated noncontributory lipiodol studies. The other was found by the simple method of withdrawing a No. 10 French catheter from the stomach while listening at the open (proximal) end. As the fistula was passed, the respiratory sounds could be heard from the open end of the catheter.

It would seem that after some experience with infants with esophageal atresia one can almost predict the failures and successes on the basis of age, weight, associated anomalies, and that immeasurable something that is tied up in what we call a "good baby." For example, there are some babies of satisfactory age and weight who have no additional demonstrable anatomic defects, but whose respirations are never properly established and whose ability to suck and swallow seems to be diminished. Other infants who appear to be good risks have such friable tissues as to preclude satisfactory anastomosis. These factors may be absent in a small series. In a large one, they combine to give a true picture of the barriers to success which the surgeon faces in a congenital anomaly incompatible with life yet theoretically susceptible to surgical correction. For these reasons, the examinations of statistics alone may not give a true indication of the difficulties presented by the anomaly or the advantages of a given technique.

We believe that transpleural approach to atresia of the esophagus, followed by direct feedings by mouth or via a polyethylene tube instead of a gastrostomy, has much to recommend it. This is true not only for the pediatric surgeon or thoracic surgeon, but perhaps more so for the occasional operator in this field. Operating time, always a factor in the care of infants, is greatly reduced. The exposure is excellent, and the number of surgical procedures is reduced. We do not believe that any of the difficulties we have encountered in the transpleural approach would have been less hard to surmount by the usual retropleural method.

SUMMARY

A series of 61 cases of esophageal atresia has been reviewed and analyzed.

Forty-two patients were operated upon by the transpleural approach with a mortality of 47.6 per cent.

The advantages of the transpleural compared with the retropleural method include: better exposure, a shorter operating time, and fewer operative procedures.

A single layer anastomosis of few sutures with early feedings by mouth seem to be associated with fewer strictures at the site of anastomosis.

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INFECTION IN BURNS

II. The Pathogenicity of Streptococci

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IT has been recognized for a long time that hemolytic streptococci frequently colonize burn surfaces. These microbes have been incriminated in burns as a cause of local invasive infection, general invasive infection with septicemia, and scarlatina. In addition, the failure of skin grafts to take and delayed healing have been ascribed to the action of streptococci. However, it was not until Jackson and his co-workers reported their data in 1951 that the deleterious effects of streptococci in burns were convincingly documented. They state that the clinical course of patients harboring beta hemolytic streptococci of Lancefield group A on their wounds is characterized by the failure of skin grafts, fever, scarlatiniform rashes, local invasive infection, increased amounts of exudation, excoriation, and unhealthy granulations.

Lyons pointed out that alpha and gamma as well as beta hemolytic streptococci are common in burns. The alpha and gamma hemolytic varieties, however, do not appear to be associated with the striking clinical findings that are typical of the beta hemolytic variety. Similarly, Lancefield groups C and D streptococci were relatively benign in comparison with the group A organisms in Jackson's study.

The primary objective of this paper is to demonstrate the effects of Lancefield group A beta hemolytic streptococci on granulation tissue that results from full thickness burn wounds, with particular emphasis on their relationship to skin grafting and, consequently, to healing time and length of hospitalization. Data will also be presented concerning the correlation of penicillin sensitivity of streptococci and Lancefield grouping.

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METHODS

Forty granulating areas of full thickness burns were studied in 20 patients. Each patient had 2 separate burns of comparable location and extent so that 40 individual wounds were studied. Some of these granulating areas were grafted more than once. In every instance, the 2 wounds of any particular patient were grafted at the same time. Altogether, 40 grafting procedures were performed in "paired wounds"; thus a total of 80 individual grafting procedures were included in the analysis. The source and age of these patients have been described previously (2). The extent of the 40 wounds studied ranged from 1 to 15 per cent of the body surface. When the study began, the mean extent of each wound was 6 per cent; the mean extent per patient was 12 per cent.

One wound in each patient was treated with an ointment containing an antibacterial agent; the other wound was treated with an ointment that did not contain any active antibacterial principle. In 13 patients, the antibacterial agent was a 1 per cent chloramphenicol ointment. In the 7 remaining patients, a furacin soluble dressing was used. Systemic chemotherapy was not given at any time while these studies were in progress. The study and conclusions concerning the effects of various agents will be presented elsewhere (3). The standardized grafting technique previously described was used (2). The first dressing change was carried out on the third or fourth postoperative day. Generally, the sutures were removed at this time, and the grafts that definitely had not taken were débrided. Areas in which the take was questionable were not disturbed. The final estimate of the percentage of take was made and recorded at the time of the second or third postoperative dressing change.

TABLE I.—RELATIONSHIP OF LANCEFIELD GROUP AND PENICILLIN SENSITIVITY OF STREPTOCOCCI

Lancefield group	Penicillin sensitivity	No.	Total
Group A	Sensitive	117	
	Resistant	0	
Group C	Sensitive	5	
	Resistant	0	
Group D	Sensitive	0	
	Resistant	78	
	Total grouped		200
Nonreacting streptococci (serologically indifferent)	Sensitive	34	
	Resistant	4	
		38	
Not grouped	Sensitive	37	
	Resistant	14	
		51	
Total grouping unknown			89
Grand total			289

Immediately after the removal of the dressings, the wounds were routinely swabbed, and the swabs were sent to the bacteriologic laboratory without delay. After the preliminary steps in culturing the organisms (2), the sensitivity of the organisms to penicillin was determined by the following method: The streptococci were isolated in pure culture on blood agar plates and tested against a penicillin solution, 40 units per milliliter, by means of a small disk of filter paper, obtained by a loose-leaf punch. The disk had a diameter of 6.5 millimeters and an absorptive power of 0.0023 milliliter; it thus contained approximately 0.092 unit of penicillin. The agar plates were incubated for a period of 18 to 24 hours at 37.5 degrees C. and examined. If the circular zone of inhibition surrounding the disk, including the disk itself, had a diameter of at least 10 millimeters, the organism tested was classified as sensitive. Lancefield grouping was performed by extraction of the "C" polysaccharide and testing with standard sera. A grafting procedure was considered to have been performed in the absence of any specified organism if the methods used failed to reveal its presence *both* at the time of grafting and at the time of the first dressing change. Isolation of an organism at either or both times was considered an association of the grafting with that particular organism.

It was decided, for the purpose of statistical evaluation of this study, that a P value of 0.01 or less would be judged "significant," a value of 0.01 to 0.05 "questionably significant," and a value of more than 0.05 "not significant."

TABLE II.—STATISTICAL ANALYSIS OF EFFECT OF STREPTOCOCCI ON GRAFT TAKES

Comparison	No.	Mean take per cent	Degrees of freedom	"t"	P
1. All group A beta strep. free cases	44	82	78	5.08	P<0.001
2. All group A beta strep. cases	36	46			
3. Group A beta strep. free cases in patients susceptible to organism	18	82	52	3.81	P<0.001
4. All group A, C, and D beta strep. free cases	34	82	41	0.37	0.7<P<0.8
5. All group D beta strep. cases	9*	78			
6. All group C beta strep. cases	2**	100	—	—	—

*1 of these wounds also yielded a group C organism.
**1 of these wounds also yielded a group D organism.

RESULTS

Penicillin sensitivity and Lancefield grouping (Table I). During the first 7 months of 1953, 289 cultures of beta hemolytic streptococci were obtained from the wounds of 52 patients. Thirty-eight culture strains failed to react to the grouping sera, and 51 additional strains were isolated before grouping methods were available. The Lancefield group was definitely determined in 200 strains. Sensitivity to penicillin was determined in all strains. All of the 117 group A culture strains were sensitive to penicillin, while all of the 78 group D strains were resistant to penicillin. The 5 group C strains were sensitive to penicillin.

Serologically indifferent streptococci. Eight grafting procedures were done in the presence of the streptococci that could not be grouped (nonreacting, serologically indifferent streptococci). In order to determine whether the 8 strains associated with these procedures could be validly considered as belonging to group A, the following analysis was undertaken: Only 5

of 122 definitely grouped, penicillin-sensitive culture strains belonged to group C; the remaining 117 belonged to group A. This represents an incidence of 4.1 per cent group C strains in the group of penicillin-sensitive organisms. The confidence limits of this percentage ($P=0.01$) is 0.9 to 11.4 per cent. Thus the risk incurred by the inclusion of penicillin-sensitive organisms that were serologically indifferent to the group A series was not great. The chances are good that all of the 8 serologically indifferent strains encountered during grafting procedures belong to group A. At worst, 1 of the 8 belong to group C, and this would not appreciably bias the results. Any bias so introduced would tend to make the group A beta hemolytic streptococci appear less deleterious than they are. As a result of these considerations, the 8 serologically indifferent streptococci are included in the group A series in the statistical analyses that follow.

Streptococci other than group A. In 9 instances, grafts were applied in the presence of group D beta hemolytic streptococci. The mean take (78 per cent) did not differ significantly from that obtained when beta streptococci were absent (82 per cent) (Table II; $t_{41}=0.37$; $0.7<P<0.8$). In 2 instances, grafting was performed in the presence of group C organisms with a take of 100 per cent in both cases (Table II). Thus, there was no evidence, in this small series, that these organisms were associated with or caused graft failure. One alpha and 2 gamma hemolytic streptococci were isolated from the various wounds concomitant with group A and group D beta hemolytic organisms.

Group A streptococci. During the period of February to June 1953, when these studies were carried out, the incidence of group A beta hemolytic streptococci among the patients was unusually high during March and April. This may be explained by the overcrowded conditions existing on the ward during that time, and by the admission of many patients evacuated from overseas who had extensive suppurating full thickness burns colonized by streptococci. In consequence, 36 of the 80 grafting procedures were performed in the presence of group A beta hemolytic streptococci, and 44 grafting procedures were done in their absence. In Figure 1 the distribution of graft takes is shown in per cent when group A beta hemolytic streptococci are present and absent. The mean takes of the two series were 46 and 82 per cent respectively, and these means differed significantly, despite the wide distribution in takes within each series (Table II, $t_{78}=5.08$; $P<0.001$).

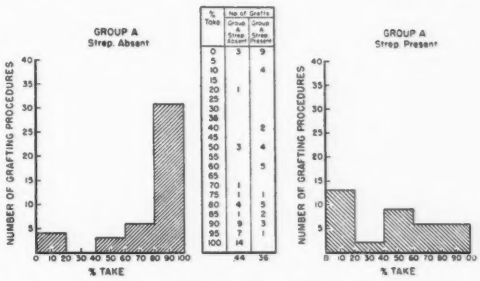

Fig. 1. Distribution of graft takes.

An objection may be raised, however, that this does not establish more than an association between the presence of group A beta hemolytic streptococci and graft failure. Streptococcal colonization of the wound and graft failure may be caused by one or more factors common to both. Debilitation, for example, might account not only for failure of the grafts to take but also for making the patient susceptible to colonization by streptococci. A comparison of cases free of group A beta hemolytic streptococci with such a debilitated series would clearly be deceptive. For this reason, another analysis was made. Attention was confined to patients who intermittently harbored streptococci on their wounds. These patients could be considered to be susceptible to streptococcal colonization. A comparison was made in these susceptible patients between all graftings done in the presence of group A beta hemolytic streptococci and graftings done in their absence. The mean takes were 46 and 82 per cent respectively and again differed significantly (Table II; $t_{52}=3.81$; $P<0.001$).

A second objection which may be raised is that the experiment described did not completely eliminate the many variables that could be responsible for the success or failure

TABLE III.—DIFFERENCES IN GRAFT TAKES DUE TO STREPTOCOCCI

Pair No.	Per cent take group A beta strep. free	Per cent take group A beta strep. present	Differences (x) (columns 2 and 3)
1	90	10	80
2	95	50	45
3	100	95	5
4	100	60	40
5	100	60	40
6	50	10	40
7	95	60	35
8	100	0	100
9	95	85	10
10	90	75	15
11	50	60	—10
12	50	10	40
Mean, per cent	(84.58)	(47.91)	36.67 ($\bar{x}$)

Standard error of mean of differences: $\sqrt{\frac{\Sigma(x-\bar{x})^2}{N(N-1)}}=8.86$

$N=12$; $t_{11}=\frac{36.67-0}{8.86}=4.14$

$0.001<P<0.01$

of the grafts to take. The following analysis was made in order to define more clearly the specific effects of group A beta hemolytic streptococci. On 12 occasions, the 2 comparable wounds of particular patients were grafted at a time when 1 wound was colonized by group A beta hemolytic streptococci while the other was free from this microbe. Factors other than the microbial flora of the wound that could influence the take of grafts, such as nutrition, immunologic responses, nitrogen balance, intercurrent respiratory infection, and so forth, were thus eliminated as variables by this experimental regimen. The influence of these factors was common to both areas. The advantages of this method, from a statistical viewpoint, have been repeatedly emphasized. The results of the statistical treatment are presented in Table III. This table shows the take of grafts applied at the same time in individual patients when group A beta hemolytic streptococci were absent and present (columns 2 and 3). In column 4, the difference in each pair of takes is shown. The mean difference between series 2 and 3 indicates that, on the average, a 36.67 per cent better take was achieved in wounds that were free from group A beta hemolytic streptococci. To determine the significance of this *mean of differences*, it must be compared with a value of zero because the mean of differences would approximate zero if group A beta hemolytic streptococci in no way influence the graft takes. The difference is significant (Table III; $t_{11}=4.14$; $0.001<P<0.01$). This finding supports the hypothesis that group A beta hemolytic streptococci are a significant cause of graft failure. A causal relationship, not merely an association, appears to be justified because of the simultaneous control provided in the same individual.

A third objection may be raised in that it might be thought that the use of various local antibiotics obscured the interpretation of the pathogenic importance of the group A beta hemolytic streptococci. These antibiotics were an incidental feature of this study and were used in connection with a broader program aimed at defining the value of local antibiotics (3). Their influence on these studies is shown in Table IV. The first comparison by differences in this table is the same as that discussed in Table III. The second series represents 12 pairs of similar recipient sites in patients who had both sites infected by group A beta hemolytic streptococci. The third series represents 16 pairs of similar recipient sites in patients in whom both sites were free from this organism. The first three series of pairs in Table IV are mutually exclusive. No cases occurred that were consistent with the fourth series listed in the table. In each series, 1 of the paired wounds was treated by administering a local chemotherapeutic agent.

The second series in Table IV indicates that the local agents, though apparently having some effect on the grafts, did not significantly influence their take in the presence of group A beta hemolytic streptococci (Table IV; $t_{11}=2.06$; $0.05<P<0.1$). This finding is consistent with the view that the streptococci exerted a predominant influence upon the outcome of a grafting procedure. The results in the third series indicate a possibly favorable action of the local agent in the absence of group A beta hemolytic streptococci (Table IV; $t_{15}=2.57$; $0.02<P<0.05$).

Appearance of wounds and systemic effects. The presence of group A beta hemolytic streptococci was associated with signs of severe local invasive infection in 4 of 12 patients who harbored this microbe on their wounds during some part of the study. Characteristic findings were: (1) increased pain; (2) disappearance of granulations with exposure of the underlying fat; (3) increased formation of a thin, grayish-yellow pus; and (4) swollen, reddened, and tender wound edges. In all of these 4 patients, there was also present undermining of the normal skin and of well healed grafts, with resultant sloughing of the undermined areas and increase in the size of the wounds. In the remaining 8 patients, the presence of group A beta hemolytic streptococci did not give rise to signs that differed from those seen in the presence of other microbes.

General invasive infection caused by group A beta hemolytic streptococci or other organisms was not observed in the patients included in this study. It must be remembered, however, that all of the patients had granulating wounds and, consequently, had reached a stage of the disease in which colonization and suppuration rather than invasive infection characteristically occurs (2).

Antistreptolysin titers. Twelve patients from whom group A beta hemolytic streptococci were isolated failed to produce more antistreptolysin than is found in serum from uninfected humans. Thus, although the streptococci were isolated intermittently from burn lesions during periods ranging up to 4½ months, and antistreptolysin tests were performed at various intervals up to 6 months after streptococci were isolated, no serum contained more than 166 units per milliliter. Possible reasons for this apparent lack of response are now being investigated.

TABLE IV.—DIFFERENCES IN GRAFT TAKES DUE TO STREPTOCOCCI AND TO LOCAL CHEMOTHERAPY

Comparison by difference in pair series	No. of pairs	Mean of differences	Degrees of freedom	"t"	P
1. Group A absent on treated site and present on control: Take of treated site minus take of control site	12	36.7	11	4.14	$0.001<P<0.01$
2. Group A present on both sites: Take of treated site minus take of control site	12	21.3	11	2.06	$0.05<P<0.1$
3. Group A absent on both sites: Take of treated site minus take of control site	16	22.5	15	2.57	$0.02<P<0.05$
4. Group A present on treated site and absent on control site	0	—	—	—	—

DISCUSSION

The association of the group A beta hemolytic streptococci and graft failure has previously been noted in an important study by Jackson and his co-workers. However, the magnitude of the difference in graft takes between wounds colonized by this microbe and those free from it was not stated. As has been observed, the demonstration of a significant difference in this connection is meaningful in a clinical sense only when the magnitude of the difference is assessed (2). Further, it had not been shown that the group A beta hemolytic streptococci actually caused graft failure. There may have been other factors that caused graft losses, such as inadequate nutrition of the patient, failing immunologic responses, exhaustion of the endocrine defense mechanisms, and intercurrent respiratory tract infections; the graft loss may, in turn, be considered the factor that favors the growth of this organism on the wound.

This study further defines the pathogenic importance of the group A beta hemolytic streptococci. When group A beta hemolytic streptococci colonize granulating burn wounds, graft failure commonly occurs. The difference of mean takes in the overall groups with and without the organism is approximately 36 per cent (Table II). This difference is not only statistically significant but also very meaningful in terms of therapy. An effort has also been made to determine whether a causal relationship exists between the occurrence of group A beta hemolytic streptococci and the failure of skin grafts to take. If all possible factors influencing the take of skin grafts could be eliminated except that of the microbe, a convincing answer could be furnished. This has been largely achieved in the study of

12 pairs of recipient sites (Table III). The significant difference for the most part is independent of the local antibacterial agent that was applied to 1 member of each pair and not to the other (Table IV).

The 9 grafts observed in the presence of group D beta hemolytic streptococci and the 2 grafts observed in the presence of group C organisms did not appear to be deleteriously affected by these organisms.

Microbes other than streptococci were present in association with all grafting procedures. Staphylococcus aureus (coagulase positive) was cultured on all but 2 occasions, and Pseudomonas aeruginosa, Proteus vulgaris, organisms of the coli-aerogenes group, and diphtheroids were isolated from the wounds in various combinations. These organisms were distributed in an apparently random fashion among the wounds colonized by group A beta hemolytic streptococci and the other wounds. The statistical techniques for the evaluation of the interaction of microbes have not yet been fully developed. Such techniques are now being studied. They are essential for the problem of interaction as well as for defining the pathogenicity of microbes that are not associated with the same striking effects as the group A beta hemolytic streptococci.

It has been reported that the group A beta hemolytic streptococci do not develop resistance to penicillin in vivo. The relationship between sensitivity to penicillin and Lancefield grouping was examined in order to ascertain whether the sensitivity of a beta hemolytic streptococcus to penicillin gives a clue as to the serologic group to which it belongs. Determination of the penicillin sensitivity of a beta hemolytic streptococcus is a satisfactory screening test for Lancefield group A organisms (Table I). Despite the fact that beta hemolytic streptococci of Lancefield group D, largely consisting of enterococci, can be cultured frequently and also have been cultured from wounds in connection with grafting, these penicillin-resistant streptococci do not appear to be associated with graft failure. In a few instances, it has not been possible to assign the penicillin-sensitive beta hemolytic streptococci to any group. This may be the result of the fact that organisms, for unknown reasons, have lost group specific precipitinogen or that the grouping sera were not sufficiently sensitive. As beta hemolytic streptococci of groups other than A, D, and C have not been found, it may be reasonable to consider these nonreacting beta hemolytic streptococci as belonging to group A since the total number of penicillin-sensitive group C organisms recovered from the burn wounds was only 5 out of a total of 200.

The implications of graft failure are manifestly evident: delayed healing, particularly in the more extensively burned patients; repeated grafting procedures; prolonged hospitalization; impaired morale of the patient and impaired function from hypertrophic scars, scar contractures, and fibrous ankylosis, to mention the more important sequelae. These complications, which may be ameliorated in part by prompt and successful grafting, have their origin not infrequently in the colonization of granulating areas by the group A beta hemolytic streptococci. The pernicious role of these bacteria have been identified by Jackson and his co-workers, and the magnitude of influence is presented here. Therefore, vigorous treatment against these organisms should be instituted in accordance with the prevailing methods of chemotherapy. Skin grafting should be performed only when the wound is free from group A beta hemolytic streptococci.

SUMMARY

1. There is a good correlation between penicillin sensitivity of beta hemolytic streptococci and Lancefield grouping. In general, beta hemolytic streptococci that were sensitive to penicillin belonged to group A. All of the group D streptococci were resistant to penicillin.

2. The mean graft take in granulating wounds colonized by group A beta hemolytic streptococci was 36 per cent less than the mean take in wounds free from these microbes. Statistical data are presented which strongly suggest that group A beta hemolytic streptococci caused the graft failure.

3. In a small number of grafts performed in the presence of group D and C beta hemo-

lytic streptococci, a deleterious effect of these microbes could not be demonstrated.

4. When granulating wounds are prepared for closure by skin grafting, cultures should be taken to determine whether group A beta hemolytic streptococci are present; if they are, every effort should be made to rid the wounds of these microbes before grafting. It is not always evident clinically that group A beta hemolytic streptococci colonize the wounds.

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CANCER OF THE BREAST

The Results of Radical Mastectomy and Radiotherapy in Two Hospitals

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THE results of treatment of cancer of the breast by radical mastectomy, with or without supplementary radiotherapy, have been published from many outstanding teaching institutions and large clinics during the last 2 decades. These results tend to reflect the combination of careful selection of cases plus the benefits of expert surgical and anesthesiologic services. Several students of the cancer problem have suggested that the results in smaller hospitals or in county hospitals are not of the same high order. As part of a continuing investigation of the place of radiotherapy in cancer of the breast, we recently reviewed the results of treatment in a consecutive, unselected series of 100 patients with primary cancer of the breast treated (mainly by radical mastectomy) at each of two hospitals in San Francisco, one a county institution and the other a private hospital. The following paper is a report and discussion of the data ascertained.

The county institution (the San Francisco Hospital) is a 1,200 bed, tax-supported, general hospital, operated by the City of San Francisco for indigent patients. The private hospital (St. Joseph's Hospital) is a 250 bed nonprofit institution operated by the Franciscan Sisters and admitting chiefly private-pay patients.

The hospital disease registries were reviewed in each institution, commencing at a date 5 years prior to the start of this particular review (that is the end of 1948). One hundred consecutive primary cases with microscopically proved cancer of the breast were listed in each hospital. All were previously untreated cases as far as the breast tumor was concerned; at the San Francisco Hospital, several were admitted because of coincidental disease or because of symptoms due to bony and other metastases. Efforts were then made to trace all of the patients to the time of their demise or, if living, up to a date at least 5 years after the date of admission or of operation; many were traced over 7 years. We were able to trace 99 per cent of the patients admitted to the San Francisco Hospital and 93 per cent of those admitted to St. Joseph's Hospital.

The San Francisco Hospital is staffed by both of the medical schools in that city, and efforts are made to admit alternate cases to each service. That this method is fairly effective is shown by the fact that 51 of the currently reviewed cases were on the Stanford University Service and 49 on the University of California Service. The writers are indebted to the surgical divisions of both these services for permission to review and report on the cases treated in each.

GENERAL FEATURES OF THE TWO SERIES

The 100 cases admitted to the San Francisco Hospital covered the period 1946 to 1948; those at St. Joseph's Hospital from 1946 to 1948.

The age distribution of the patients at the San Francisco Hospital was 28 to 90 years, and at St. Joseph's Hospital, 32 to 91 years.

The clinical and pathologic staging of the cases seen at the San Francisco Hospital showed that many patients with more advanced disease were admitted to this county institution than were sent to the private institution. Indeed, the number of stage III and stage IV lesions seen at the private institution during the period under review was so small that it became apparent that many were treated as outpatients. Some were referred for radiotherapy to various radiologists in the city; others were treated as office patients with steroid hormones. In other words, the material presented herewith represents in each

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instance 100 consecutive cases actually *admitted* to each hospital.

All cases were microscopically proved; at the San Francisco Hospital the slides were reviewed by members of the Departments of Pathology of Stanford University Medical School and the University of California Medical School. At St. Joseph's Hospital the tissues were reviewed by the staff pathologists, frequently in collaboration with the chief of the surgical staff, a long time student of the histopathology of breast lesions.

An attempt was made to stage all cases clinically according to the common modification of the Portmann classification[1]; this clinical staging was revised, when necessary, by the microscopic findings at operation. The following is based, therefore, predominantly on microscopic staging: The San Francisco Hospital patients included 22 stage I cases, 27 stage II, 51 stages III and IV; the St. Joseph's Hospital series included 37 stage I, 60 stage II, and 3 stages III and IV cases.

There is no question but that staging is the most important single factor in the prognosis of breast cancer. This fact has been well demonstrated in a careful long term study of 1,044 cases of primary breast cancer seen at St. Bartholomew's Hospital in London between 1930 and 1940, of which 97.1 per cent were followed up. Interestingly enough, *the clinical staging in this particular series of cases proved as reliable for purposes of prognosis as the pathologic* (Table I).

TABLE I.—CANCER OF THE BREAST

No. of cases in clinical stages in different series

	I	II	III	IV
Williams *et al.* (1,044)	33	29	27	10
Shimkin *et al.* (1,056)	32	28	30	10
Smithers (769)	22	32	29	17
San Francisco Hospital (100)	22	27	51	
St. Joseph's Hospital (100)	37	60	3	

ASSESSMENT OF RESULTS

There are many ways of assessing the apparent results of treatment of breast cancer, the most satisfactory being 20 year, age-standardized, complete follow-up curves. It is well known that many cases of breast cancer recur after being apparently arrested for 5, 10, and even 15 years. Nevertheless, it is not always possible to express results in such desirable long term figures. Reasonable comparison may be made with results obtained in other clinics by indicating the origin of the cases, staging the cases, and recording the 5 year survival data. Some of these 5 year survivals will have persistent or recurrent cancer at the time of reporting; some will develop recurrent cancer at variable times thereafter. Bearing these facts in mind, 5 year survival data do permit deductions as to the *trend* of "results" in any given clinic or hospital. For purposes of expressing results in percentages it would be desirable to have at least 100 cases in each of the stages, and that all cases be followed. These desiderata are obviously not possible of fulfillment in the present report.

RESULTS OF TREATMENT

In the 100 consecutive cases of primary cancer of the breast admitted to the San Francisco Hospital between 1944 and 1948 all but 1 case was traced. The single untraced case was a patient with stage III disease who was given only palliative treatment; she is counted as dead of disease.

The treatment was as follows: radical mastectomy in 39 cases (16 of these had postoperative radiotherapy); simple mastectomy in 9 cases (7 of these had postoperative radiotherapy); radiotherapy alone in 20 cases (mainly palliative); no treatment to the primary site in 32 cases. The reasons included terminal disease, patients with grave complicating disease, and 2 patients who refused medical treatment on religious grounds.

Of the 22 cases in stage I, 2 were not treated for the breast lesions, which were incidental to more serious conditions present; 14 of the remaining 20 were alive and well at 5 years (70 per cent).

Of the 27 cases in stage II, 2 were not treated owing to complicating cardiac disease or religious factors; 10 of the remaining 25 were alive at 5 years (40 per cent)—all but 1 well.

Of the 51 cases in stages III and IV, 22 were so advanced or had such complicating cardiac,

[1]Stage I is a cancer localized to the breast without involvement of skin, nodes, or deeper structures. Stage II included similar cases, but with some axillary node involvement. Stage III includes cases with skin involvement, satellite tumors, fixed tumors, and extensive axillary node involvement. Stage IV consists of cases with evidence of distant metastases.

TABLE II.—FIVE YEAR SURVIVAL IN TREATED CASES

Stage		I	II	III and IV
S. F. H.	No. of cases	20	25	23
	5 year survival	14	10	1
	Per cent survival	70	40	4
S. J. H.	No. of cases	37	59	2
	5 year survival	24	25	0
	Per cent survival	65	42	0

cerebral, or other disease, that no treatment was given them for the primary breast condition. Thirty cases were given local treatment, mainly palliative; 1 of these was alive at 5 years, a patient who was treated by radiotherapy alone.

It is of interest to note that 3 of the 9 patients treated by simple mastectomy were well after 5 years, and 1 for almost that length of time; these cases are as follows:

1. Case 3. Age 58 years, stage III lesion. Simple mastectomy and postoperative radiotherapy. Survived 4½ years; developed recurrence and died.
2. Case 4. Age 63 years, stage II lesion. Simple mastectomy and postoperative radiotherapy (tumor dose about 3,750 r in 3½ weeks). Living and well 6 years. Simple operation done because of cardiac status and anesthetic reaction.
3. Case 34. Age 53 years, stage I lesion. Simple mastectomy and postoperative radiotherapy (tumor dose about 3,000 r in 4 weeks). Living and well 8 years. Simple operation done under impression lesion was a benign cyst.
4. Case 49. Age 81 years, stage I lesion. Simple mastectomy and preoperative radiotherapy (tissue dose about 1,000 r in 4 days). Died of independent disease 8 years later. Simple procedure done on account of patient's age.

In summary, therefore, 25 out of 100 patients admitted (or 25 of 68 cases given treatment to the primary site) were alive at 5 years.

When the treated cases are considered by stages, it is evident that 14 of 20 cases in stage I were arrested (70 per cent), and 10 of 25 in stage II (40 per cent). Combining both stages, 24 of 45 (53 per cent) survived.

In the 100 consecutive cases of primary cancer of the breast admitted to St. Joseph's Hospital between 1946 and 1948, all but 7 were traced. These 7 consist of 4 patients with stage I and 3 with stage II disease; 2 were known to be well at 4 years and 2 at 3 years. However, for purposes of this report, all 7 are counted as dead of cancer.

The treatment was as follows: radical mastectomy in 91 cases (9 of these had postoperative radiotherapy); simple mastectomy in 5 cases (2 of these had postoperative radiotherapy); radiotherapy alone in 2 cases; biopsy alone in 1 case; no treatment to primary site in 1 case (the metastases were treated).

Of the 37 cases in stage I, all were treated; 24 patients survived 5 years (65 per cent). Two of them had persistent or recurrent disease at the time of review.

Of the 60 cases in stage II all but 1 were treated; 25 patients survived 5 years (40 per cent). Three of them have persistent or recurrent disease.

Of the 3 cases in stages III and IV, 1 was untreated; none of the 3 survived 5 years.

In summary therefore, in the material at St. Joseph's Hospital: 49 of 100 admitted cases (or 49 of 98 cases given treatment to the primary site) survived 5 years.

When the treated cases are considered by stages, it is noted that 65 per cent of the stage I and 42 per cent of the stage II cases survived for 5 years. Combining both stages, 49 of 98 treated cases (or 50 per cent) survived. This is essentially the same survival rate as was obtained at the San Francisco Hospital.

If the cases with known persistent or recurrent disease at 5 years are deducted, then 23 of 45 cases (51 per cent) were "arrested" or clinically "cured" for 5 years at the San Francisco Hospital, and 44 of 98 cases (45 per cent) at St. Joseph's Hospital. Since postoperative radiotherapy was used much more extensively at the San Francisco Hospital, one is tempted to conclude that the slight difference in arrest rates may be attributed to such. However, the number and type of cases seen is not sufficient for valid conclusions regarding this point.

TABLE III.—FIVE YEAR SURVIVALS

Treated cases	S. F. H.		S. J. H.	
	No.	Per cent	No.	Per cent
Stages I and II	24	53	49	50
Stages I to IV	25	37	—	"50"*

*Stages III and IV treated elsewhere.
1 S. F. H. and 5 S. J. H. survivals at 5 years have recurrent or persistent disease.

MORTALITY AND MORBIDITY

There was no mortality ascribable to the radical operation in this particular series of 200 cases. The operation was the more or less "conventional" radical procedure, that is, no attempts were made at en bloc excision of the mediastinal tissues, internal mammary nodes, or supraclavicular nodes.

The morbidity was difficult to estimate. It is our impression that about 15 per cent of the patients subjected to the radical operation had significant edema of the arm; however, the number of patients carefully examined after 5 years is not as great as we would like. Conversely, including a small group of cases treated elsewhere during this review period, only about 3 per cent of those submitted to simple operation had such; again, the number of cases in this group is too small for true percentage figures. Weakness of the arm on the side of the radical operation was often marked. Delayed healing and occasionally painful scars were sequelae of wide skin removal.

DISCUSSION

The problem of the treatment of breast cancer is the treatment of all cases, not just the operable ones. If only the truly operable or surgically curable ones are considered, a high percentage of these will be arrested for 5 years by radical mastectomy and a high surgical "cure rate" will be obtained, but the overall results will be relatively poor. This is illustrated by Smithers as follows:

Results of radical mastectomy. Assuming 100 unselected cases, of which 55 per cent are stages I and II, and 45 per cent are stages III and IV. Also that 70 per cent of stage I and 40 per cent of stage II survive 5 years.

Stage	I	II	III	IV
No. in stage	25	30	30	15
Absolute 5 year survival rate, per cent	70	40	20	2
Survived	18	12	6	

Total No. of survivors: 36

His survival rates in stages I and II are rather similar to the absolute survival rates obtained at the San Francisco Hospital (at which institution some of the patients also received additional radiotherapy); these are as follows:

Stage	I	II	III and IV
No. in stage	22	27	51
Absolute 5 year survival rate, per cent	64	37	2
Survived	14	10	1

Total No. of survivors: 25

Now, if we consider only the group given some form of treatment in the San Francisco Hospital series, the relative survival rate figures (but not the actual number of survivals) naturally improve:

Stage	I	II	III and IV
No. in stage treated	20	25	23
Relative 5 year survival rate, per cent	70	40	4
Survivals	14	10	1

Total No. of survivors: 25

By the use of a program of simple mastectomy and vigorous postoperative radiotherapy applied to almost all cases seen, McWhirter has been able to secure an increased survival rate in those cases with cancer spread beyond the breast; the rate for those patients with disease still confined to the breast is naturally the same by simple as by radical operation. His material gives this picture:

Results of simple mastectomy and radiotherapy. Assuming 100 unselected cases, of which 55 per cent are in stages I and II and 45 per cent in stages III and IV.

Stage	I	II	III	IV
No. in stage	25	30	30	15
Absolute 5 year survival rate, per cent	58		29	4
Survived	32		9	1

Total No. of survivors: 42

We have co-operated in the use of McWhirter's technique in a small group of 13 cases to date. These, combined with the cases treated by simple mastectomy and postoperative ra-

TABLE IV.—COMPARISON OF 5 YEAR RESULTS OF TREATMENT

Author and year	Absolute survival rate, per cent	Relative survival rate, per cent
McWhirter (1949)	41	43
Adair (1949)	35	37
Smithers (1952)	35	35
Siris and Dobson (1946)	33	39
S. F. H. series Garland *et al.*	25	37

diotherapy at the San Francisco Hospital lead us to believe that his conclusions are correct. A small but definite improvement in the 5 year survival rate is achieved by the simple operation plus radiotherapy program.

SUMMARY

Two series of 100 consecutive primary cases of breast cancer in women admitted to two hospitals in San Francisco are reported. Ninety-nine per cent of one series and 91 per cent of the second series were traced.

The principal form of treatment was radical mastectomy.

The 5 year survival rates in both institutions were quite similar when the results were analyzed by stage of disease. However, since one series included 51 patients with stages III and IV lesions, while the other included only 3 patients with such advanced disease, the absolute or overall results in the two institutions were quite dissimilar.

The relative 5 year survival rates were 70 and 65 per cent respectively in the two hospitals for cases of stage I disease; they were 40 and 42 per cent respectively for cases of stage II disease.

Considering all patients given some form of treatment to the primary lesion, the relative survival rates were 37 and 50 per cent respectively. The difference in these figures is due to the presence of many cases of more advanced disease in the first institution.

The present series of cases did not permit any conclusions as to the merits of postoperative radiotherapy in cases of stage II breast cancer. However, the results in general are slightly inferior to those obtained by McWhirter, using a combination of simple mastectomy plus vigorous postoperative radiotherapy as the major form of treatment. It is to be noted that most of the figures published by McWhirter deal with absolute results, that is, are based on all patients seen with the disease whether accepted for treatment or not. The material in this paper deals largely with relative results, that is, on the basis of only those patients admitted to a hospital for treatment. The fact that these relative results are not considerably better than McWhirter's absolute results tends to speak in favor of his method.

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THE REACTION OF THE WALL OF A VEIN TO INTRALUMINAL BLOOD CLOT

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IT HAS long been recognized that there is a marked variability in the degree of inflammatory reaction in the walls of veins that harbor thrombi. In some instances this inflammatory reaction is marked and it is thought by some, gives rise to physical signs and symptoms to which the diagnostic term thrombophlebitis has been applied. In other cases little or no change is seen in the wall of a vein even though its lumen may be completely occluded by a thrombus. The process of thrombosis may thus be unattended by other signs or symptoms and a diagnosis of phlebothrombosis is commonly rendered.

The significance of this inflammatory reaction is not clear. It is possible that it is the primary event in thrombophlebitis and that the thrombus develops in the lumen as a result of the inflammation in the wall. On the other hand Allen, Barker, and Hines[1] in discussing the problem state "A thrombus may develop without previous inflammatory changes in the wall of the vein, but if the thrombus remains in the vein for more than a few hours, secondary phlebitis also develops as a reaction to the thrombus." "Thus," they continue, "phlebothrombosis as defined by Ochsner and DeBakey exists as such only for a short time and then the condition actually becomes a thrombophlebitis."

The present work was undertaken in an attempt to determine if a thrombus lodged in a normal vein would incite an inflammatory reaction. At the outset, an effort was made to produce in the dog a thrombus which might bear resemblance to the type found in man, and to introduce this thrombus into a vein in the animal's leg, and to arrest it at a point where its effect could be observed. Difficulties in the production of a thrombus without the use of strong chemical or physical trauma and in the technique of introducing and later arresting the thrombus without traumatizing the host vein have led us, for the present, to abandon our original intent. Instead, our investigation has involved the effect of simple blood clot (as opposed to thrombus) introduced into a venous system (the portal system) in which the passage of the clot would be automatically checked without the application of a ligature or other external pressure which might, by itself, induce an inflammatory reaction.

Accordingly, a technique has been developed and carried out in a series of dogs as follows.

TECHNIQUE

Fifteen milliliters of blood are removed from a dog the night prior to operation. This blood is placed in a sterile test tube and allowed to stand at room temperature. Twelve hours later, the dog is anesthetized with intravenous nembutal, 1 milliliter per 5 pounds

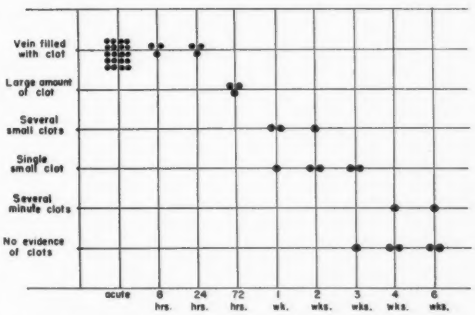

Chart 1. Graphic representation of the amount of clot found in the animals sacrificed at various intervals and indicating the gradual disappearance of the injected clot.

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[1]ALLEN, E. V., BARKER, N. W., and HINES, E. A. JR. Peripheral Vascular Diseases. Chap. XXV, p. 585. Philadelphia, London: W. B. Saunders Co., 1040.

Fig. 1.

Fig. 4.

Fig. 2.

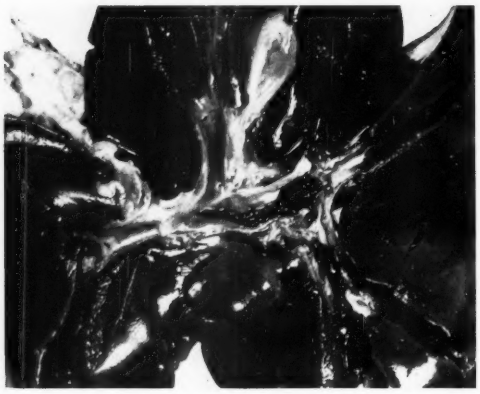

Fig. 3.

Fig. 1. Acute. Liver dissected immediately after injection into the splenic vein showing the main branches of the portal vein completely filled with clot.

Fig. 2. Liver examined 24 hours following injection of clot into the splenic vein showing vein still filled with clot.

Fig. 3. Liver examined 72 hours following injection of clot showing a large amount of clot remaining in the larger radicles.

Fig. 4. Liver examined at 1 week, showing several small clots in the larger branches of the portal vein.

of body weight. The abdomen is opened and the spleen brought out through the incision. A large branch of the splenic vein in the mesentery of the spleen is isolated and ligatures passed about it. A cannula is inserted and the retracted clot obtained from the previously removed blood sample, the volume of which usually amounts to some 6 milliliters, is injected through this cannula. The passage of the clot through the cannula results in a worm-like mass of clot passing into the splenic vein. In order to assure that this technique would result in a filling of the portal vein in the hilus of the liver, 22 dogs were examined immediately following the injection. In all but 2 instances it was found that the vein was filled, and in these 2 it was recognized beforehand that the injection had not been properly carried out. In the survival experiments, groups of 3 animals each were sacrificed at the following intervals: 8 hours, 24 hours, 72 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, and 6 weeks. At the time of sacrifice, the liver, pancreas, and spleen were removed *in toto* and their vessels thoroughly

Fig. 5.

Fig. 6.

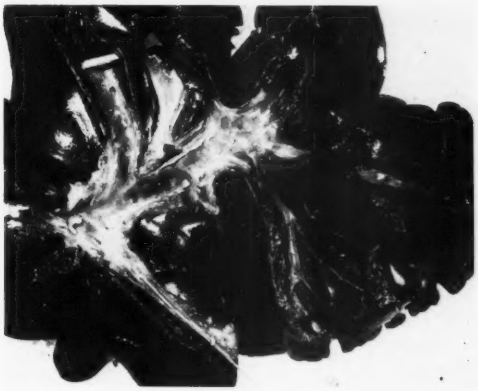

Fig. 7.

Fig. 5. Liver examined at 2 weeks, in this instance, small clots present in the main branch of the portal vein. In 2 other specimens examined at 2 weeks, there was considerably less clot present.

Fig. 6. In a liver examined at 3 weeks, the only finding is a small mass of clot adherent to the intima in the region of bifurcation of one of the branches of the portal vein within the liver.

Fig. 7. Two of the animals examined at 6 weeks showed no evidence of clots. The liver in this case showed some minute depression on the intimal surface. Microscopic examination of these areas did not reveal any evidence of residual clot or inflammatory reaction.

dissected. The amount of residual clot in each case was noted, and sections in various parts of the portal vein of the liver itself were taken for histologic study.

FINDINGS

Acute dogs. In every instance, except 2 in which the technique of injection was recorded as unsatisfactory, the portal vein was found to be completely filled with clotted blood. The vein was similarly found to be filled with clot in the animals that were sacrificed at 8 and 24 hours following injection.

Survival dogs. Findings in animals sacrificed at later periods are best shown graphically in Chart 1 and Figures 1 to 7 which illustrate the gradual disappearance of the clot in the portal veins of these injected animals. It will be noted in the chart and the photographs that the clot which, at the outset, fills the largest portion of the portal vein and its radicles in the liver gradually disappears over a period of time, eventually in all instances leaving practically no trace. In none of the animals examined was there, at any time, any naked eye evidence of inflammatory reaction in the portal vein, the intima being clear and glistening except in those instances in which there was roughening at the site of attachment of the remnants of the clot.

HISTOLOGICAL FINDINGS

Dogs which were killed 8 and 24 hours after the injection of clot showed no reaction in the walls of the portal veins (Fig. 8).

At 72 hours there was slight or dubious lymphocytic infiltration of the adventitia of veins occupied by clot.

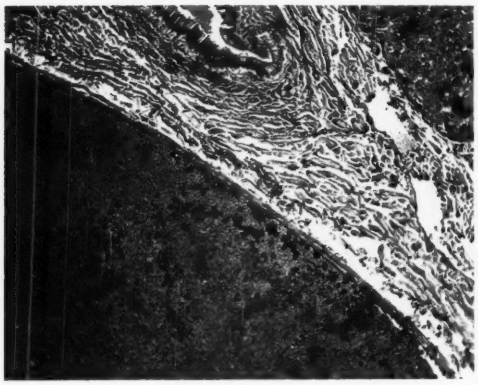

Fig. 8.

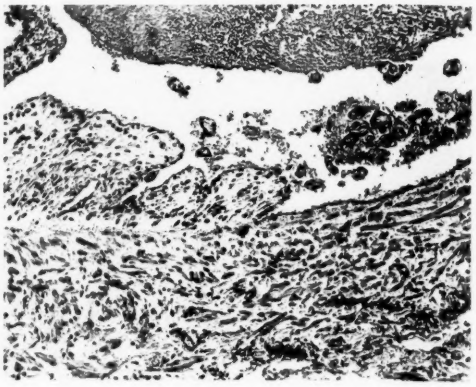

Fig. 9.

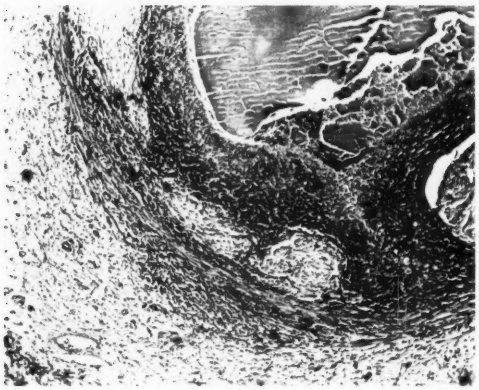

Fig. 10.

Fig. 8. Showing clot after 24 hours with no reaction in the portal vein.

Fig. 9. Two weeks after injection showing small masses of granulation tissue attached to the intima.

Fig. 10. Three weeks after injection. Shows marked inflammation.

At 1 week when the clot was greatly diminished in volume, endothelialization was present over the remaining material. Comparatively narrow points of attachment were demonstrated in some cases with various degrees of organization and early fibrosis of the clot. In most instances, the vein wall showed very little reaction. This consisted of a sparse infiltration by lymphocytes and interruption of all coats by thin-walled capillaries passing to the organizing clot.

At 2 weeks organization had increased to form fibrous masses or intimal plaques (Fig. 9). Some small clots still showed a relatively large amount of unorganized protein-like material.

The vein wall at the point of attachment of the clot showed some interruption of the muscle by fibrous tissue. In the remainder of the circumference of the vein no abnormality was noted.

One dog killed at 3 weeks showed the most marked alterations seen in this series. Nothing was seen in the larger veins, but there was complete obstruction of several of the smaller veins, the largest measuring approximately 1.5 millimeters in diameter and the smallest 0.5 millimeter. These veins were occupied by masses consisting of endothelioid cells, lymphocytes, and polymorphs together with various degrees of fibrosis and some masses of protein-like material containing hemoglobin, presumably the remains of the clot. The walls of these veins showed dense infiltration by lymphocytes and fibroblasts and this inflammatory reaction spread into the adjacent connective tissue (Fig. 10). Special stains showed no bacteria. This was the only dog in the whole series in which a severe inflammatory reaction was present. One of the other 2 dogs killed at 3 weeks showed no residual clot and the other a small fibrotic

organized mass without any surrounding inflammation.

Dogs killed at 4 weeks and 6 weeks showed no abnormality.

In addition to the sections made of the large branches of the portal vein in which the clots were known to lodge after injection, numerous blocks were examined from more peripheral portions of the livers in an attempt to detect evidence of embolism by small detached masses of clot.

The 3 weeks dog with the marked reaction was the only animal showing abnormality of relatively small veins, and in no case was there any abnormality of the liver parenchyma attributable to the experimental procedure.

In a few dogs abnormalities which appeared to be due to natural disease were found. These included pericholangitis and in 1 dog a definite helminth infection with a polymorphonuclear reaction.

CONCLUSIONS

It is concluded from the findings that simple retracted blood clot introduced into the portal vein system of a dog piles up in the portal vein immediately, has no apparent serious effect upon the health of the animal, and gradually disappears without leaving any gross evidence of inflammatory reaction in the vein. Histologic studies have revealed minimal inflammatory reaction in some instances, and considerable inflammatory reaction was found in only 1 specimen examined in which a small branch of the portal vein was found to be completely blocked.

CARCINOMA OF THE STOMACH ASSOCIATED WITH PERNICIOUS ANEMIA

A Clinical and Pathologic Study

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FROM the standpoints of incidence and the discouraging results of surgical treatment, cancer of the stomach poses one of the most serious problems facing the medical profession today. Its cause remains obscure and the early symptoms are often so nondescript that much valuable time is lost in arriving at an early diagnosis. Much of the literature of the past two decades concerns an inordinately high incidence of gastric carcinoma arising in patients with clinical pernicious anemia. It was with the idea of studying a relatively large group of patients with this complication that the present study was undertaken.

BACKGROUND INFORMATION

Addison in 1849 (1, 2) and again in 1855 and Biermer in 1871 described the entity now known as pernicious anemia. Cancer of the stomach had been known ever since Hippocrates stated that black vomitus had a bad prognostic significance. On the basis of chance alone the two conditions should occasionally coexist, and the first report of such a combination by Quincke, in 1877, probably came as no surprise to his colleagues. However, when men like Konjetzny began studying the gastric mucosal changes in patients with pernicious anemia and predicting an increased incidence of gastric carcinoma among those who could survive for long periods with the anemia, investigators began taking sides on the issue.

The late H. E. Robertson was among the group who championed the idea that the grossly flattened (atrophic) gastric mucosa seen in cases of pernicious anemia coming to necropsy was in many cases microscopically hyperplastic with intestinalization of the mucous cell elements. He stoutly maintained that when therapy succeeded in carrying large numbers of patients with pernicious anemia into the "cancer age," we would see an alarming increase in this malignant complication.

Following the work of Minot and Murphy and of Castle and others, therapy with liver extract came into general use in the early 1930's. By 1938, Cotti was able to collect reports of 107 cases of cancer complicating pernicious anemia. Significantly enough, 93 of these were examples of gastric cancer. Moreover, 65 per cent of these cases were reported in the literature in the period 1930 to 1938.

In an extensive study by Rigler and Kaplan, 45 instances of gastric carcinoma were found in a series of 293 patients dying of pernicious anemia, an incidence of approximately 15 per cent. In a comparable study of 212 living patients with a diagnosis of pernicious anemia the incidence of coexisting gastric carcinoma was 8 per cent, and gastric polyps were found with about the same frequency. The transformation from clinically benign polyp to metastasizing carcinoma sometimes occurred with surprising rapidity.

Earlier experiences at the Mayo Clinic more or less paralleled the findings of Rigler and Kaplan. These experiences were reported by Olson and by Judd. In Olson's series, neoplastic complications were twice as common among patients encountered subsequent to 1929 as they were among those encountered prior to that date.

The recent literature contains an increasing number of reports of gross and microscopic

Abridgment of thesis submitted by Dr. Schell to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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udies on the gastric mucosa of patients with astritis, both in the presence and absence of ernicious anemia. These studies follow the ne of attempting to verify or deny the existnce of precancerous alterations. The results these studies will be correlated with our ndings.

MATERIAL AND METHOD

The records of all Mayo Clinic patients on hom the clinical diagnosis of both pernicious emia and carcinoma of the stomach was ade during the period 1906 through 1950 re studied. After subjecting all the cases analysis concerning the validity of the diagses, 94 were selected and were divided into o groups. Group 1 was composed of 48 es in which the gastric lesion was excised, d group 2 consisted of 46 cases in which no rgical procedure or only exploratory lapotomy was done (Table I). The data from the latter group were, of course, somewhat incomplete, but were utilized in order to obtain as unbiased a picture as possible. In future paragraphs, unless otherwise indicated, the data pertain to group 1, also referred to as the surgical group.

In each case from group 1, the entire resected portion of the stomach was available for review. This tissue was examined grossly and microscopically with special attention to the gross appearance (Borrmann's classification), the position and local involvement of the tumor, and the appearance of the surrounding mucous membrane with regard to the preservation of mucosal folds and the presence of mammillations. Strips of mucosa, both near to and remote from the tumor, and a section of the tumor were taken for microscopic study. The malignancy was graded according to the method of Broders. The sections of mucosa were studied with special attention to the degree and type of gastritis and to the degree and type of the hyperplastic changes in the mucous cells. Since the degree of gastric mucosal atrophy in almost all the sections of fundic mucosa would be classified as severe, the suggestion of Warren and Meissner was followed and the epithelial changes were differentiated from the inflammatory component.

TABLE I.—DISPOSITION OF CASES FROM THE STANDPOINT OF SURGICAL TREATMENT

	Cases	Per cent
Definitive operation	48	51.1
Resection (considered palliative in 9, or 23.1 per cent, of the resections)	39	41.5
Segmental resection or transgastric excision	9	9.6
Exploration only	22	23.4
Exploration plus gastroenterostomy	1	1.1
Esophagoscopy with dilatation or biopsy, or both	2	2.1
Operation not advised (inoperable by x-ray, poor surgical risk)	15	16.0
Patient refused operation	6	6.4
Total	94	

CLINICAL FINDINGS

In this series there were 67 males and 27 females, giving a ratio of 2.5 to 1. The average age was 55.1 years at the time of diagnosis of pernicious anemia and 61.7 years at the time of diagnosis of carcinoma.

In group 1 the two diseases were diagnosed simultaneously or in less than a year of each other in 15 cases (31.2 per cent), many of the gastric lesions being found incidentally by roentgenologic examinations made because of the diagnosis of the anemia. In 24 cases (50 per cent) diagnosis of the anemia preceded diagnosis of the carcinoma by 1 to 23 years, and in the remaining 9 cases (18.8 per cent) the diagnosis of the anemia was made 1 to 8 years after the gastric operation. However, in several of these cases symptoms of the anemia existed prior to operation, but the true hematologic picture had been obscured by a superimposed loss of blood from the gastric neoplasm.

PATHOLOGIC CHANGES

Gross changes (Figs. 1 and 2). In all the 48 surgical cases there was gross flattening of the folds in the uninvolved mucous membrane which varied in degree from moderate to complete effacement. In addition, in the fundic region in all cases there were varying numbers of mammillations—small "warty" elevations on the mucosa which on section proved to be hyperplastic islands of intestinalization. In some cases these were almost large enough to

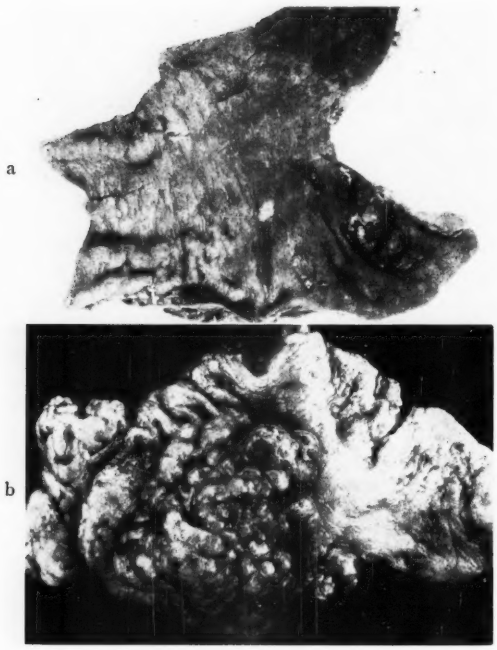


Fig. 1. Carcinomas discovered at the time of, or before, the diagnosis of pernicious anemia. a, Man aged 53 years. Carcinoma was picked up incidentally by x-ray examination at the time of diagnosis of pernicious anemia. Flattening of antral mucosal folds, mammillations, line of demarcation between the fundus and antrum, and the presence of multiple (2) polypoid carcinomas are demonstrated. The larger polyp was the site of grade 1 and grade 3 adenocarcinoma. b, Man aged 65. Carcinoma was present 4 years prior to anemia. A large, polypoid fundic tumor and rather marked mammillations of uninvolved mucosa are evident. The lesion proved to be of low grade 2, with admixture of grades 1 and 2 (see also Fig. 3b).

suggest sessile polyps. In areas where several of these mammillations were aggregated almost to confluence, foci of in situ carcinoma were found microscopically (discussed later).

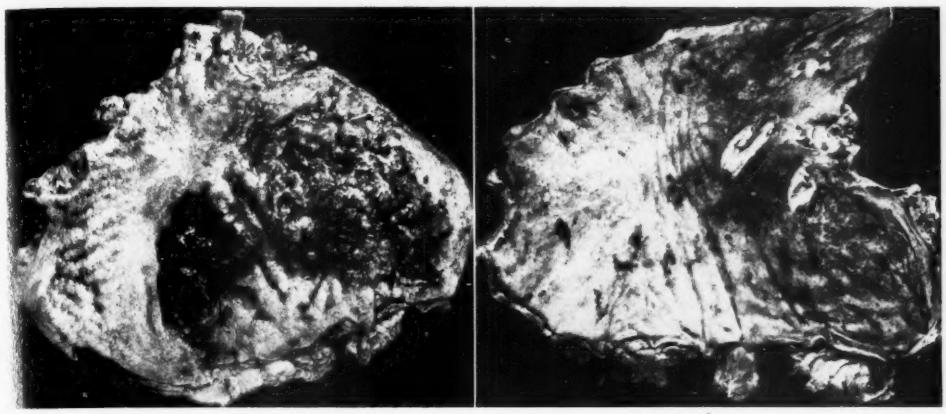
The Borrmann method of typing tumors was found to be relatively satisfactory, except that many of the large polypoid tumors had ulcerated in the center and would thus, in a strict sense, have fallen into his second type. Accordingly, in our study the polypoid and ulcerated-polypoid tumors were lumped together, but the tumors of types III and IV were separated out. There was an unusually high percentage of polypoid tumors (81.3 per cent were types I and II).

In view of the marked tendency of the gastritis of pernicious anemia to localize in the fundus and cardia, it was of interest to note the position of the tumor in the stomach. The tumor was located in the pyloric antrum in only 27.1 per cent of the cases, whereas it was found in the fundus and cardia in 58.3 per cent. In the remaining 14.6 per cent there were either separate tumors in both areas, or 1 tumor involving both, so that the origin was difficult to determine.

The frequency with which multiple malignant tumors occurred in this series was most surprising (Figs. 1a and 2a). In 13 cases (27.1 per cent) of group 1, more than 1 tumor was found, and in each of 2 cases, 3 apparently separate tumors were encountered. Some of these consisted of microscopic areas of malignant growth and will be discussed later. In all, 63 carcinomas were found in the 48 cases. In addition, 1 myosarcoma of the gastric wall was encountered in association with an intragastric adenocarcinoma. Benign mucosal polyps were associated with the carcinomas in 3 cases (6.3 per cent).

Microscopic changes (Figs. 3 to 8). Mucosa.—For the purpose of this study the microscopic changes in the gastric mucosa were classified into two groups: (1) the inflammatory component, which consisted of scatterings and collections of lymphocytes, irregular thickening of the muscularis mucosae with occasional trapping of glandular elements beneath it (Fig. 4), and thinning of the mucosa; and (2) the epithelial element, which consisted of decrease in the number and depth of the glandular tubules, "intestinalization" with the presence of goblet cells (Fig. 3a), atrophy of the chief and parietal cells with relative increase in the number of mucous cells, and hyperplasia of cytologically malignant-appearing mucous cells—the secondary cytoplasia of MacCarty (Fig. 5b). Unless these malignant-appearing cells could be proved to the reviewer's satisfaction to have escaped the lamina propria of the gastric glands (Fig. 7c), the area was considered benign.

The two last-mentioned changes, namely hyperplasia of mucous cells and secondary cytoplasia, do not fall into our usual concept of gastritis. Consequently, in this study, they



a b

ig. 2. a, Man aged 63 years. Multiple carcinomas are nt. The average grades were 2, 3, and 4, respectively, ough 1 tumor showed a mixture of all grades. Carci- was diagnosed 10 years after pernicious anemia. rcinoma en plaque in a man aged 61. Total gastrectomy was performed. The entire fundus in the lower half of the picture is involved, and the carcinoma underran the esophagus. The lack of thickening of the mucosa is well demonstrated at the points where the biopsy specimens were taken (see also Fig. 8).

e singled out to be recorded separately. A inction between these two changes in mucous cells is probably artificial, both apparently being a process of exuberant regeneration or repair of damaged mucosa. These changes will be reported as epithelial hyperplasia, whereas the remaining elements are listed under the generic name "gastritis."

A rather surprising finding in 8 of the cases in which resection was done early in the course of the pernicious anemia (in the sense that the pathologic changes in the stomach probably far antedated the clinical symptoms) was the presence of subacute gastritis with a scattering of parietal cells remaining in the sections (Fig. 3b).

The gastritis was graded mild, moderate, severe, or subacute. In no case, even in the pyloric antrum, was there complete absence of inflammatory changes. However, as would be expected from previous reports, the sections from the fundus showed more severe changes than did those from the antrum. The fundic sections in which the changes were classified severe represented the type generally reported at necropsy in cases of pernicious anemia. In many of the present cases the gastritis was not this marked and was graded moderate. The term subacute was used when the mucosa appeared edematous and was infiltrated with large numbers of inflammatory cells other than lymphocytes. Sparsely scattered parietal cells were usually to be found in these cases, although achlorhydria had been a constant finding.

The epithelial hyperplasia was graded mild, moderate, or severe. Mild indicated that there were only scattered fields in which the changes were noted. Moderate indicated that in at least 1 of every 3 microscopic fields the mucosa was so affected. Severe was used when change was visible in almost every field, up to long strips of mucosa in which every gland would have to be studied to rule out the presence of mucosal cells in the interglandular stroma.

The findings regarding gastritis and epithelial hyperplasia are given in Table II. As can be seen, there is a higher correlation between the severity of the hyperplastic changes and the presence of the tumor in a specified segment than is found when comparing the degrees of gastritis in the cancerous and noncancerous portions.

The antrum never completely escaped all changes, but the gastritis was never graded severe and the epithelial hyperplasia was severe in only 6 cases. In 3 of the cases in which the fundus was involved in subacute

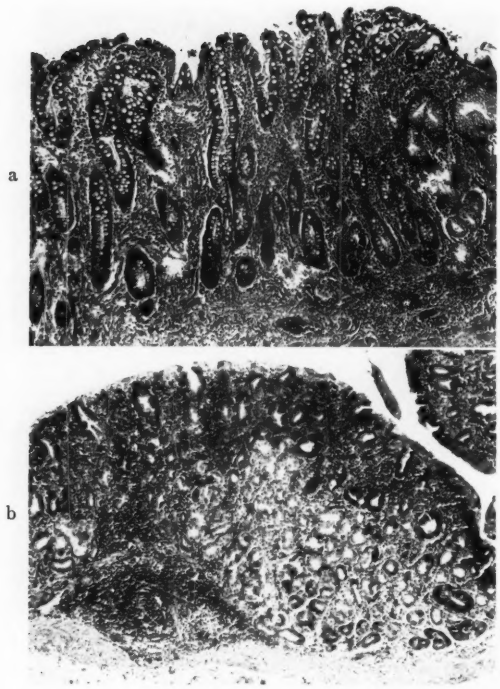


Fig. 3. a, Man aged 60 years in whom pernicious anemia and gastric carcinoma were diagnosed simultaneously. Intestinalization extends to the bottom of the glands. The section was photographed with a green filter so that the eosinophilic Paneth cells in the depth of the glands appear black. Several Russell bodies are shown to the left side of the picture. Hematoxylin and eosin, ×37. b, (Same case as Fig. 1b.) Carcinoma 4 years prior to anemia. There is evidence of subacute gastritis, with parietal cells visible in fair quantity in the section. Hematoxylin and eosin, ×55.

gastritis the antrum seemed to have been spared.

Undoubtedly the most striking finding was that in only 1 specimen from the fundus was the epithelial hyperplasia graded mild; in all other cases the change was frequent enough to be graded moderate or severe. All the sections taken from the tumor and surrounding mucosa showed a severe grade of epithelial hyperplasia with little increase in the inflammatory component. Since this finding did not vary from case to case, it was not believed necessary to include it in the tabulation. It is, however, of interest to note that the mucosa surrounding all the microscopic areas of carcinoma,

TABLE II.—DATA ON GASTRITIS AND EPITHELIAL HYPERPLASIA IN GROUP 1 CASES

	Antral mucosa* with						Fundic mucosa† with					
	Antral tumor		Fundic tumor		Both		Antral tumor		Fundic tumor		Both	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Gastritis												
Mild	8	21	13	34	3	8	0	0	0	0	0	0
Moderate	3	8	5	13	1	3	6	14	4	9	3	7
Severe	0	0	0	0	0	0	6	14	15	34	2	5
Subacute	2	5	2	5	1	3	1	2	6	14	1	2
Epithelial hyperplasia												
None	0	0	6	16	0	0	0	0	0	0	0	0
Mild	4	11	7	18	4	11	1	2	0	0	0	0
Moderate	5	13	5	13	1	3	6	14	6	14	4	9
Severe	4	11	2	5	0	0	6	14	19	43	2	5

*Tissue available in 38 cases.
†Tissue available in 44 cases.

which were discovered entirely by chance in the routine sections of the fundic mucosa, were always involved in severe epithelial hyperplasia, more frequently of the secondary cytoplasia type than of the benign hyperplasia type. It is difficult to visualize how an area of carcinoma 1 to 2 millimeters across could have already "caused" these changes in several square centimeters of surrounding mucosa.

Tumors.—In the 48 cases of group 1 we obtained data on 63 carcinomas, including the multiple tumors found in 13 cases. These were graded according to Broders' method (Table III). In many of the cases, the tumors were found to represent a mixture of grades, several running the gamut from grade 1 to grade 4. In order to tabulate these cases, the most predominant type was given as a sort of average for purposes of analysis.

To avoid, as much as possible, inaccuracies caused by selection of cases, the microscopic slides which were available in 15 cases of group 2 were also reviewed. It would appear that the grades of the inoperable carcinomas did not differ appreciably from the grades of those in which resection was completed except in the slightly higher incidence of grade 3 carcinomas, although the validity of conclusions based on such a small series is open to criticism. There was a suggestion that the tumors

TABLE III.—CARCINOMAS GRADED ACCORDING TO BRODERS' METHOD

Grades	Group 1*		Group 2*		Total
	No.	Per cent	No.	Per cent	
1	21	33.3	3	20.0	24
2	20	31.7	4	26.7	24
3	17	27.0	7	46.7	24
4	4	6.3	0	0.0	4
Totals	62		14		76

*Also there was 1 case (1.6 per cent) of small cell carcinoma in group 1, and 1 case (7.1 per cent) in group 2.

Borrmann's types III and IV tended to be slightly higher grade than those of Borrmann's types I and II.

One of the most interesting findings in this study was the detection of microscopic areas of carcinoma unconnected with gross tumefaction in 6 cases (Fig. 7). Four of these fulfilled all the criteria for multiple carcinomas and were found at a distance of several centimeters from the gross lesion. In the other 2 cases the lesions were close enough to the large tumor that a connection, although not demonstrated, could possibly have been present; consequently only the 4 are classified as multiple carcinomas. It is of great interest to speculate that if these microscopic areas of carcinoma were found entirely at random in 4 of 48 cases, how many could be found by a careful scrutiny of the entire uninvolved mucosa?

Another interesting finding was the discovery of 2 cases of carcinoma en plaque in which areas of the mucosa more than 5 centimeters in diameter were involved in a carcinomatous change without gross evidence of tumefaction (Figs. 2b and 8). Both of these tumors were graded 3; 1 had involved areas in the submucosa, while the other appeared to be confined entirely to the mucosa above its muscularis layer.

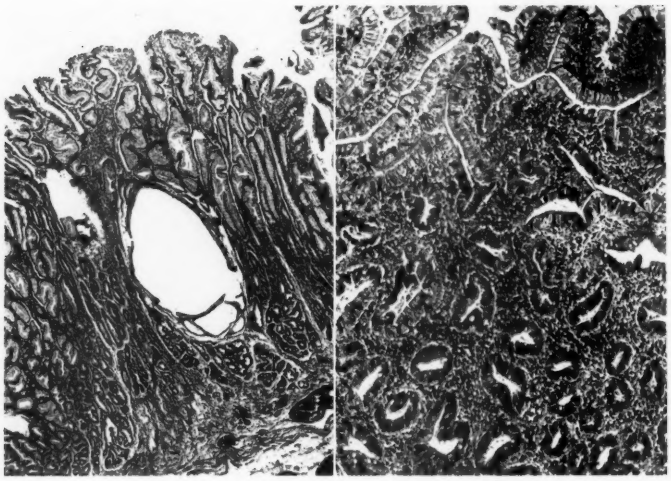
COMMENT

The age at which pernicious anemia apparently occurred in our series of cases was somewhat greater than the average age of patients with pernicious anemia, and it may be that the older patient in whom this disease develops warrants more careful watching. The average age at the time of diagnosis of carcinoma in our series was likewise somewhat higher than the average for gastric cancer in general. It would appear that many more cancers may be found at the time of initial diagnosis of the anemia than at any given later date. This finding explains why, in a follow-up examination of Kaplan and Rigler's patients reported by State and co-workers, no further lesions were noted. The increase in the number of cases after 1930 is worthy of note: from 1906 to 1930, 5 cases in group 1 and 3 in group 2; from 1931 to 1935, 9 cases in group 1 and 9 in group 2; from 1936 to 1940, 10 cases in group 1 and 10 in group 2; from 1941 to 1945, 8 cases in group 1 and 13 in group 2; from 1946 to 1950, 16 cases in group 1 and 11 in group 2—a total of 48 cases in group 1 and 46 in group 2.

Fig. 4. Man aged 64 years. Pernicious anemia was diagnosed 2 years prior to carcinoma. Trapping of a gland beneath the muscularis mucosae, one of the elements of gastritis, is demonstrated. Hematoxylin and eosin, ×111.

The gross findings in the mucosa do not differ greatly from those in any case of severe pangastritis. The presence of many mammillations, especially where they tend to be congregated in a relatively small area, should put the pathologist on his guard for a possible multicentric origin of carcinoma, and should this finding be noted by the surgeon in an unresected portion of the stomach, it would appear that biopsy is definitely warranted.

The high incidence of polypoid tumors and their tendency to occur in the fundic and



a b

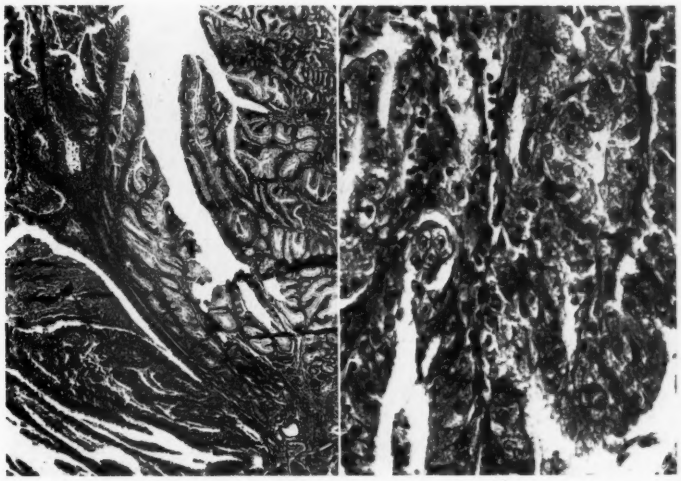
Fig. 5. a, Woman aged 63 years. Carcinoma was diagnosed 8 years before anemia. Epithelial hyperplasia of the type known as "cytologically benign appearing mucous cell hyperplasia" and also cyst formation with distention of a gland are depicted. Hematoxylin and eosin, ×22. b, Man aged 62. Pernicious anemia and carcinoma of the stomach were diagnosed simultaneously. This is a low power view of an area of extensive secondary cytoplasia. Note the loss of the basal position of the nuclei, large nucleoli, and irregularity of the glandular lumina. Hematoxylin and eosin, ×74.

cardiac region are borne out by this study, and appear significant since ordinarily about 75 per cent of gastric carcinomas arise in the antrum. It would seem wise, when a patient with pernicious anemia is examined for gastric lesions, to forewarn the radiologist concerning the anemia so that an especially careful search of the cardiac region—long known as a blind region for the radiologist—can be made. Emphasis should also be placed on the polypoid nature of the carcinomas so that only the surgical pathologist will be allowed to differentiate the benign from the malignant polyps in pernicious anemia. The present-day low mortality rate from gastric operations does not warrant any program of watchful waiting when such a lesion has been discovered.

The finding of multiple carcinomas in 27.1 per cent of the cases in group 1 is certainly worthy of note, as the frequency of this finding reported in a study by Hansbro of all gastric cancers from the Mayo Clinic was only 1.45 per cent. This tends to give supportive evidence to those who believe that the gastric mucosa in pernicious anemia is prone to undergo malignant change, and perhaps it even supports the theory that the particular picture of the gastritis seen in these cases is indeed indicative of a premalignant lesion.

There is a possibility that we have, in the finding of subacute gastritis, a picture of the intermediate stage of atrophy of the stomach, the end point of which has been seen previously in cases encountered at necropsy. The route taken and the mechanism still remain to be worked out, and may come with the increasingly frequent use of biopsy of gastric mucosa. Case 2, reported in a subsequent portion of this paper, is of particular interest in this regard.

The finding of a high percentage of cases in which there was severe gastritis in the fundus, with less severe changes in the antrum, does not warrant further discussion as it has been well documented previously. The striking evidence of epithelial hyperplasia, however, does. The fact that cytologic changes are difficult to detect in necropsy material is probably one reason why this has not been stressed in previous studies of the gastritis of pernicious



a b

Fig. 6. Man aged 64 years. Pernicious anemia was diagnosed 8 years prior to carcinoma. a, Transition from benign-appearing hyperplasia (right) to anaplasia (left) is shown. Hematoxylin and eosin, ×22. b, Detail of anaplasia in a section taken from the left lower corner of a. Hematoxylin and eosin, ×222.

nemia. MacCarty considered the lesion precancerous when found around gastric ulcers, but apparently did not believe that secondary cytoplasia occurred in chronic gastritis. Ewing's and Mallory's more recent reports of carcinoma in situ are of interest in this connection. It is not being suggested here that hyperplasia and secondary cytoplasia are in themselves carcinomatous lesions, since no one knows how frequently these changes can revert to produce normal-appearing mucous cells; however, it is suggested that this type of reaction to injury may be the mechanism whereby the cells fall all the way over to anaplasia. It is certainly difficult to look at the cells without becoming suspicious, as their confinement within the lamina propria appears to be the chief histologic evidence that they are not, in truth, cancer cells. The finding of microscopic areas of true carcinomatous change at significant distances from the tumor as well as the high incidence of multiple carcinomas—both indicating multicentricity of origin of cancers—supports the statement made.

REPORT OF SELECTED CASES

CASE 1. A man, 62 years old, had had "indigestion" most of his life. He had experienced none of this difficulty from 1925 to 1928, but then he had a recurrence which became gradually worse, and he lost 20 pounds prior to the time he was seen at the Mayo Clinic in May, 1929. At that time an extensive carcinoma of the lower half of the stomach was diagnosed by roentgenograms, and at operation a tumor measuring 9 by 16 centimeters was removed by a high Polya type of resection. The tumor proved to be of mixed grades 1 and 2, with 1 lymph node being involved. The convalescence was uneventful. Eight years later, in 1937, the diagnosis of pernicious anemia was made, and the patient was treated with liver extract, with good response. He was reported to be living and in good health in January, 1951, at the age of 83 years.

The sections taken from the uninvolved fundus in the foregoing case revealed a subacute gastritis very similar to that depicted in Figure 3b.

CASE 2. A woman, aged 48 years, came in September, 1934, for the diagnosis and treatment of severe attacks of pain in the right upper quadrant of the abdomen associated with nausea, vomiting, and jaundice. The concentration of hemoglobin was 8.4 grams per 100 cubic centimeters of blood, and there were 3,160,000 erythrocytes per cubic millimeter. The preoperative diagnosis was cholecystitis with probable choledocholithiasis. At operation on September 11, 1934, a contracted gallbladder was found, and choledochostomy revealed stones in the common duct. An incidental finding was a firm, nodular mass in the pyloric region of the stomach,

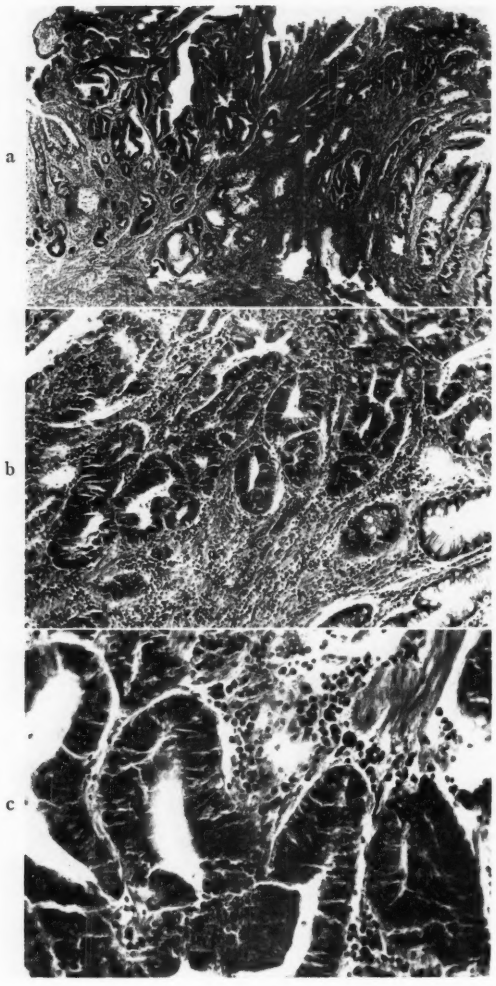


Fig. 7.

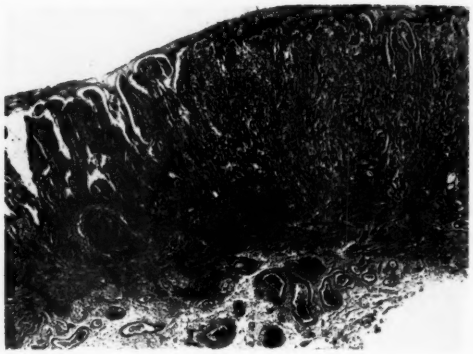


Fig. 8.

Fig. 7. Man aged 62 years. Pernicious anemia was diagnosed 3 years prior to carcinoma. a, A microscopic area of cancer was found 4 centimeters from the main tumor in a routine section of fundic mucosa. The entire width of the carcinoma appears in this field. Hematoxylin and eosin, ×22. b, Detail from the upper right corner of a showing transition from gastritis with severe intestinalization (lower right) through severe secondary cytoplasia (center) to obvious carcinoma (upper left). Hematoxylin and eosin, ×74. c, Detail from the left center of b showing severe secondary cytoplasia with beginning evidence of escape of mucous cells from the lamina propria. Hematoxylin and eosin, ×185.

Fig. 8. Man aged 60 years. Carcinoma en plaque and pernicious anemia were diagnosed simultaneously. There is a layer of desquamated cells adherent to the surface of the tumor, which gave the area a whitish appearance. The area of the carcinoma was 5 centimeters in diameter. Hematoxylin and eosin, ×22.

so that a subtotal gastric resection of the Polya type was done. Pathologic examination revealed a grade 3 adenocarcinoma involving the pylorus, with no nodal involvement.

About a year later, in September, 1935, the patient returned because of failure to gain strength since the operation and because of paresthesias in the feet and legs of about a week's duration. Careful questioning disclosed that she had had glossitis for about 2 years. The value for hemoglobin was 9 grams, the erythrocyte count was 2,660,000, and a blood smear was typical of pernicious anemia. The patient responded well to treatment with liver extract.

Eleven years later, in August, 1946, the patient was seen because of a recurrence of epigastric distress, anorexia, and loss of weight. Gastric roentgenograms revealed a cancer in the remaining portion of the stomach. Re-exploration was carried out on August 26, 1946, and an almost total gastrectomy was performed. Pathologic examination disclosed that no cancer was present at the line of the previous resection, but that 3 distinct polyps were present on the lesser curvature; the malignancy of the polyps was graded 1, 2, and 3 respectively. The patient died 2 days after the second resection was performed.

Case 2 presented a veritable museum of pathologic findings. In the material from the fundus taken at the first resection, subacute gastritis and also a microscopic area of anaplasia, confined to the mucosa 4 centimeters from the original growth and classified as grade 1 adenocarcinoma, were noted. In addition to these findings, there was severe epithelial hyperplasia. In the material from the second resection, the gastritis was much more typical of the atrophic type of pernicious anemia, but still severe epithelial hyperplasia was present, and again a grade 1 adenocarcinoma was found in a routine section of the fundus 4 centimeters from the nearest tumor. The lack of involvement of the line of resection, the demonstrated multicentricity of the tumor, and the interval between the cancers would lead one to believe that the entire gastric mucosa in this case was predisposed to carcinomatous change, and points up the problem of adequate resection. The finding of subacute gastritis at the first resection, with an atrophic picture 12 years later, is also of interest.

SUMMARY AND CONCLUSIONS

The study reported in this paper was based on the clinical data recorded in 94 cases in which pernicious anemia and carcinoma of the stomach occurred together, and on the material obtained at gastric resection in 48 of these cases. The cases were encountered at the Mayo Clinic during the period 1906 through 1950. No effort was made to undertake a statistical analysis of incidence. On the basis of this study the following conclusions are offered:

1. A gastric carcinoma in a patient with pernicious anemia differs from the usual gastric carcinoma in that it tends to be (a) polypoid, (b) fundic or cardiac in origin, (c) multicentric, (d) of lower average grade, (e) of a mixture of grades, and (f) very late in causing symptoms owing to the constant achlorhydria and fundal position which often characterize the tumor.

2. The greater predominance of fundic lesions, the multicentricity of areas of cancer formation, and the evidence of epithelial hyperplasia found throughout the fundus all tend to question the adequacy of subtotal gastric resection in such cases.

3. The diagnosis of pernicious anemia is, in itself, ample justification for initial, and probably also for follow-up, roentgenographic examination of the stomach.

4. The late average age at diagnosis of pernicious anemia in the cases of this series suggests that the patient in whom the anemia develops late in life warrants more careful observation.

5. Only the surgical pathologist should be allowed to decide whether a polypoid gastric lesion in a case of pernicious anemia is benign or malignant.

6. Gastrotomy, thorough inspection, and perhaps biopsy should be done at an exploratory operation in cases of pernicious anemia if a gross tumor is not apparent, since only in this way will a carcinoma en plaque be discovered.

7. The diagnosis of pernicious anemia when a gastric carcinoma is developing concomitantly is sometimes obscured by hypochromic anemia.

8. Epithelial hyperplasia, as defined herein, is a constant finding in areas involved in carcinomatous change, and this is suggested as being one of the steps of anaplastic transformation.

9. Subacute gastritis may well be one of the stages through which the gastric mucosa passes prior to presenting the appearance of atrophic gastritis.

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TRANSPORT OF RADIOACTIVE COLLOIDAL GOLD BETWEEN SEROUS CAVITIES

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RADIOACTIVE colloidal gold has been used for a number of years in the treatment of various intra-abdominal neoplasms with coexisting ascites. The palliative or possible therapeutic effects derived from the administration of Au^{198} have been documented in the studies of Andrews (1), Storaasli, and others. The present study, in addition to therapy, offered a unique opportunity to investigate the transport of particulate matter between serous cavities. This portion of the study was promoted in part by interest of the investigators in the dynamics of the so-called Meigs' syndrome and the many conjectures concerning coexistent hydrothorax and ascites.

SUBJECT OF PRESENT STUDY

The patient, a 61 year old, gravida 2, para 2, was admitted to the hospital for proctologic investigation because of a history of rectal pain and bleeding. On questioning, the patient stated that she had noted mild, lower abdominal discomfort and abdominal "bloating" for several months. For the past 3 weeks, she complained of progressive loss of appetite and a persistent nonproductive cough. The physical examination showed an alert, cooperative, moderately obese, very pallid white female. A soft, blowing apical diastolic and systolic murmur was present. The abdomen was distended with a "crown of tympany on a base of dullness." A fluid wave could be demonstrated, and an irregular suprapubic mass could be palpated. Bimanual examination showed the pelvis to be occupied by a firm, irregular, fixed mass, extending laterally to the pelvic walls and superiorally to the umbilicus. Laboratory studies were within normal limits except for red blood count of 3 million and a hemoglobin of 7.6 grams. A flat x-ray plate of the abdomen demonstrated an upward displacement of the colon with ascites. No intrinsic bowel lesion was disclosed by barium enema. X-ray studies of the chest showed bilateral pleural effusion and a small diaphragmatic hernia. The clinical diagnosis was ovarian carcinoma with ascites and hydrothorax (Meigs'-like syndrome).

Two preoperative bilateral thoracocenteses were productive of 2,160 and 1,650 cubic centimeters of slightly sanguineous fluid containing cells suspicious of malignant change. Laparotomy 8 days following admission revealed a large, semisolid, friable, cystic mass involving all of the pelvic structures, small bowel, and mesentery. A large amount of bloody ascitic fluid was present. The abdomen was closed after biopsy because of the profuse bleeding encountered on manipulation of the tumor mass. It was identified as a liposarcoma of mesenteric fat (Figs. 1 and 2). The ascitic fluid contained malignant cells.

Following blood transfusions and conservative therapy of an ileus, the patient made an uneventful postoperative recovery, except for the rapid reaccumulation of ascitic and pleural fluid. In an attempt to repress the ascitic fluid formation and the tumor growth, it was decided to use radioactive colloidal gold. Because of the coexisting fluid in both the abdominal and pleural cavities, three additional speculative features were decided to be investigated coincidentally: (1) Would radioactive colloidal gold be transported from the abdomen to the pleural cavity as were the carbon particles in Meigs' case? If this took place, the Au^{198} would provide a substance that could be quantitatively measured. (2) Provided that abdomen to chest transport could be demonstrated, would the converse, or chest to abdomen transport, occur using a

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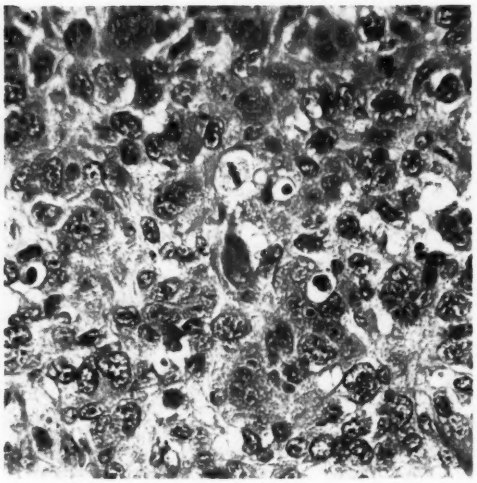

Fig. 1. Low power view of cellular portions of the tumor. Note mitotic figure near the center of the field and the multinucleated cell at top.

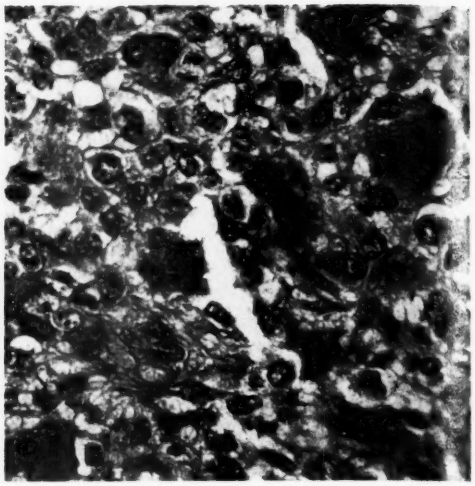

Fig. 2. Giant nuclei and multinucleated cells are demonstrated. Note that the cytoplasm of many of the cells is vacuolated.

similar technique and material? (3) Would the abdominal administration of Au^{198} have an effect on the formation of the pleural fluid? These studies could be made without interfering with any palliative or therapeutic effect of the radioactive gold.

TECHNIQUE FOR TRANSPORT STUDIES

Following a paracentesis in which 800 cubic centimeters of very bloody fluid were withdrawn, a therapeutic dose of 150 millicuries of radioactive colloidal gold diluted with 200 cubic centimeters of isotonic saline was administered intraperitoneally. Five specimens, 5 cubic centimeters each, were withdrawn from the right pleural cavity at 2, 5, 11, and 22 hours. A total thoracentesis producing 1,175 cubic centimeters of bloody fluid was performed at 46.5 hours.

The specimens were analyzed for radioactivity by a liquid counting method and comparison to an aliquot of the original dose. Correction for radioactive decay is automatic by this method and the concentration was determined in terms of per cent of dose per cubic centimeter for each specimen.

The concentration of Au^{198} in the specimens withdrawn at various times is presented in a semilog plot in Figure 3. The average concentration was .30 by 10^{-2} per cent of dose per cubic centimeter and a total of 3.4 per cent of the dose administered intraperitoneally was recovered by thoracentesis from the right pleural cavity 46.5 hours later.

All of the specimens contained radioactive material and a relatively high concentration appeared in the pleural fluid as early as 2 hours after the intraperitoneal administration. The considerable variations in concentration may be due to the physiologic dynamics of the transport mechanism, fluid formation, the site of withdrawal, or improper mixing of the fluid in the cavity.

The study of transport from the right pleural to the peritoneal cavity was carried out 8 weeks after the peritoneal to pleural study which provided ample time for decay of abdominally administered Au^{198}. Five peritoneal taps, removing a total of 12,800 cubic centimeters of fluid, were required in the interim. Thoracentesis at this time produced 300 cubic centimeters of dark bloody fluid from the right pleural cavity. Immediately following this procedure, 56.8 millicuries of radioactive colloidal gold diluted with 100 cubic centimeters of isotonic saline were ad-

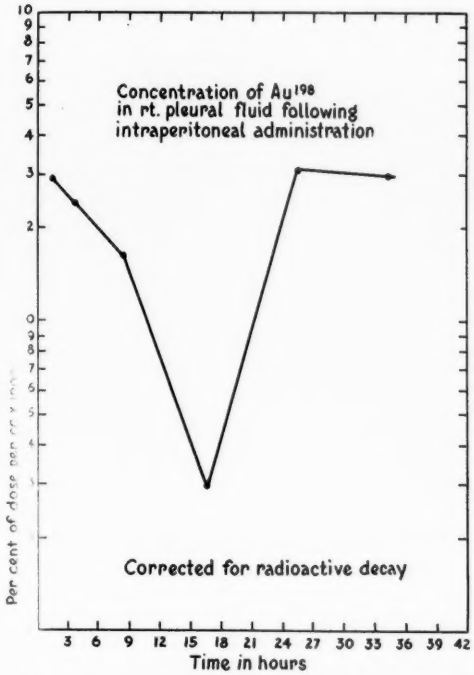

Fig. 3. Concentration of radioactive gold in pleural fluid following intraperitoneal administration. Values corrected for radioactive decay and plotted on semilog paper.

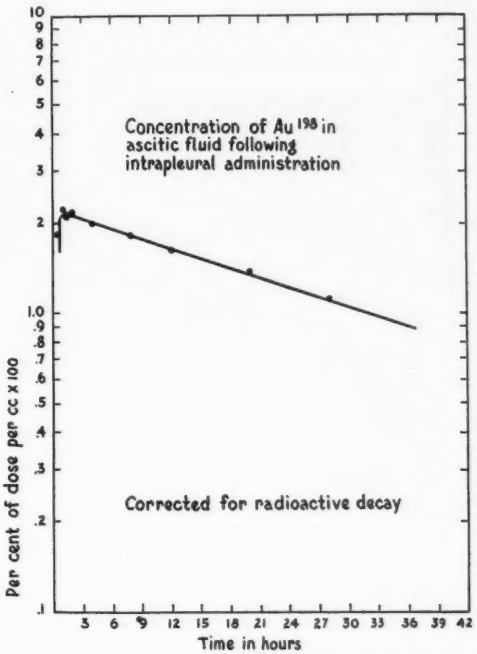
Concentration of Au198 in
ascitic fluid following
intrapleural administration
Corrected for radioactive decay
Per cent of dose per cc x 100
Time in hours

Fig. 4. Concentration of radioactive gold in ascitic fluid following intrapleural administration. Values corrected for radioactive decay and plotted on semilog paper.

ministered into the cavity. Specimens of fluid from the peritoneal cavity were withdrawn by means of a small polyethylene tube which remained in the cavity. Samples were taken at .5, 1.0, 1.5, 2.0, 4, 8.0, 12.0, 20.0, and 28 hours following the administration of gold to the right pleural cavity. The cavity was then allowed to drain overnight. A total of 490 cubic centimeters of dark bloody fluid was withdrawn.

Each specimen was analyzed for radioactivity as described before. The concentration of Au^{198} in terms of per cent of dose per cubic centimeter for the specimens withdrawn at the various times is presented in the semilog plot in Figure 4. The average concentration was 1.1 by 10^{-2} per cent of dose per cubic centimeter and a total of 5.5 per cent of the dose administered to the right pleural cavity was withdrawn from the peritoneal cavity approximately 40 hours later. Since a paracentesis cannot be complete, an indeterminate amount remained in the cavity.

The concentration of radioactive gold in the ascitic fluid reached a maximum within 1 hour after the intrapleural administration. The concentration decreased exponentially with time. Assuming the fluid volume to remain constant during the study, the rate of decrease in concentration is such that one-half of the radioactive material would be removed from the free fluid in about 36 hours. As indicated by Andrews (2), this rate of decrease is typical of a dose of Au^{198} injected directly into the peritoneal cavity wherein the gold is removed from the free fluid by phagocytosis and deposited on the serous walls.

Of the radioactive material withdrawn, 65 per cent appeared in the supernatant fluid after centrifugation; 35 per cent was included in the residue. However, since the residue volume constituted only 5 per cent of the

total volume, the concentration in the cell mass was approximately 10 times as great as that in the supernatant fluid.

If the volume of fluid can be considered constant, then it may be stated that approximately 11.5 per cent of the pleurally administered dose was delivered to the peritoneal cavity within 1 hour and that after 40.0 hours, 6.0 per cent was deposited on the serous walls and 5.5 per cent recovered in the final paracentesis.

CONCLUSIONS

1. There was a rapid transport of the radioactive colloidal gold (Au^{198}) from the peritoneal cavity to the pleural space. A maximum concentration was obtained within 2 hours.

2. Radioactive gold was found in the abdominal cavity following right pleural space administration with a maximum concentration in 1 hour. The concentration of Au^{198} in the abdominal fluid decreased exponentially with time, the rate of decrease being typical of Au^{198} that is injected directly into the abdominal cavity.

3. Little or no therapeutic effect on the development of ascites was obtained in the case of this patient. The pleural fluid reaccumulation seemed, however, to be slightly repressed.

4. The concentration of the transported Au^{198} was found to be 10 times greater in the cell mass than in the supernatant fluid.

5. The dynamics of transport of radioactive gold between serous cavities is a matter of conjecture. However, the per cent of dose delivered to the opposite cavity in each instance contraindicates a direct communication, since the amount is not proportional to the volume of fluid in each cavity. The differences in the concentration of the gold in other body fluids, e.g. blood, urine, feces, do not indicate the blood stream as the carrier. Therefore, some form of rapid transdiaphragmatic lymphatic transport appears as the most feasible explanation for the results obtained in this study.

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MICROSCOPIC STRUCTURE OF GASTRIC CARCINOMAS AND THEIR REGIONAL LYMPH NODES IN RELATION TO SURVIVAL

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THE variable behavior of the same type of cancer arising in different individuals has long been an enigma, and many attempts have been made to establish criteria which would explain or predict why one cancer patient succumbs 6 months postoperatively while another survives 10, 20, or 40 years only to die of the disease at that time. Among such prognostic systems has been the grading of the primary tumor according to the microscopic evidence of anaplasia or the extent of the operable neoplasm at the time of surgery. These systems, while serving as rough prognostic guides, frequently fail to explain why appreciable numbers of patients with inoperable cancers may experience long survivals while in presumably favorable cases death from the disease occurs in a short period of time. Such observations have suggested that the biologic behavior of cancer depends not only on factors related to the primary growth but also upon factors in the host.

That such host factors might be reflected by the microscopic structure of the regional lymph nodes in breast cancer was suggested by a previous study (1). Thus, we found that in approximately 40 per cent of cases of breast cancer the axillary lymph nodes showed dilation and filling of the sinusoids by a proliferation of large histiocytes. This finding was associated with an almost universal survival and apparently represented a readily demonstrable expression of a type of host resistance which was significantly correlated with the biologic behavior of cases of breast carcinoma.

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In addition it was previously observed by Moore and Foote that the occurrence of lymphocytic infiltrate and follicle formation in breast carcinomas was associated with improved survival periods. Further, we observed that survival in cases of breast carcinoma with minimal sinus histiocytosis of the regional nodes was correlated with the degree of differentiation of the primary tumor (2).

In view of these observations it was pertinent to inquire as to the incidence of such findings in the primary tumor and regional lymph nodes of cancers in other locations and what relationship, if any, could be demonstrated between them and survival. We, therefore, undertook an investigation of the microscopic structure of gastric carcinomas and their regional lymph nodes with particular reference to survival. The data obtained indicate that superior survival figures in operable cases of gastric carcinoma are associated with the presence of a lymphocytic infiltration or follicular metaplasia in the primary tumor and/or sinus histiocytosis of the regional nodes. These features appear to be more critically related to survival than the age or sex of the patient, the gross or microscopic growth pattern of the tumor, the duration of preoperative delay, or the presence or absence of regional node metastases at the time of surgery.

MATERIAL AND METHODS

For the purpose of this study we have compared the microscopic structure of the primary tumor and regional lymph nodes as well as certain pertinent clinical data in two selected series of cases of gastric carcinoma. One of the series included 54 patients known to have survived 5 years or longer postoperatively (5

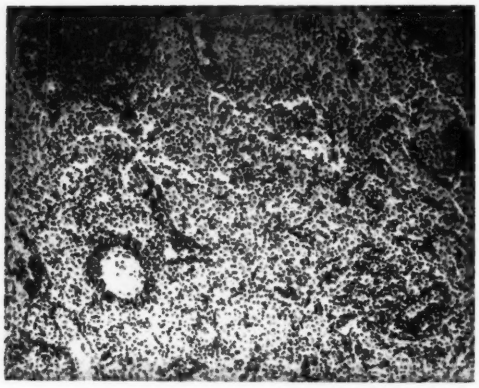

Fig. 1. Regional lymph node. Markedly dilated sinusoids filled with histiocytes; 4 plus sinus histiocytosis. ×68.

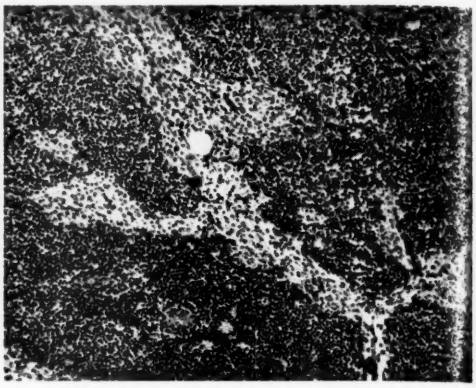

Fig. 2. Regional lymph node. Sinus histiocytosis 2 plus. ×68.

year cures)[1] while the other included 66 patients with operable carcinoma of the stomach known to have died within 3 years of operation (death series). This latter group was chosen in a consecutive fashion from the surgical pathology files only those patients who experienced operative deaths being eliminated.

The lymph nodes were evaluated, as previously reported (1), according to the degree of sinus histiocytosis and follicular prominence, with the intensity of such reactions being graded from 0 to 4 plus.

A 4 plus sinus histiocytosis is characterized by prominent sinusoids throughout the lymph node, the sinusoids being filled in a compact fashion with large cells having an eosinophilic cytoplasm and vesicular nuclei. Many of the nuclei show a definite nucleolus (Figs. 1 and 2). In contrast a 0 degree of sinus histiocytosis is said to occur when such proliferation of sinus histiocytes is absent, either because the sinusoidal structure per se is minimal or absent or the sinusoids are dilated and prominent but filled only with lymph and scattered lymphocytes, polymorphs, or lipid laden histiocytes.

A 4 plus follicular reaction is characterized by a diffuse prominence of hyperplastic follicles having secondary centers. Such follicles often show coalescence between two or more adjacent follicles (Fig. 3). As indicated in our previous report, the secondary centers may be composed of a compact arrangement of fibroendothelial cells or aggregates of lymphoblasts and lymphocytes. In contrast a 0 degree of follicular hyperplasia is said to exist when the node shows minimal or no differentiation in regard to follicle formation and no secondary centers.

It should be mentioned that where variability in the structure of different nodes from the same case was encountered the grading was made according to the findings in the node with the greatest degree of follicular and sinusoidal reactions.

The primary tumor was studied in regard to its gross and microscopic growth pattern as well as the type of associated stromal reactions encountered. The stromal change

[1]All except 7 of these cases were obtained from the files of the Department of Surgical Pathology, Presbyterian Hospital.

TABLE I.—PER CENT INCIDENCE OF THE DEGREE OF SINUS HISTIOCYTOSIS OF REGIONAL LYMPH NODES IN OPERABLE GASTRIC CARCINOMA

Degree of sinus histiocytosis	Per cent dead within 3 years (66 cases)	Per cent 5 year cures (48 cases)
0	72	62
+1	22	9
+2	5	15
+3	2	13
+4	—	2
Mean	0.35	0.85

which appeared to be of particular significance in the present study was the finding of a lymphocytic reaction in the primary tumor. This occurred in two forms which most often but not always paralleled one another; (a) a lymphocytic infiltration in and around the primary tumor (Figs. 4 and 5) and (b) the appearance of lymph follicles, many of which showed secondary centers. These follicles were associated with the primary tumor or located in the adjacent mucosa and deeper submucosa and muscularis (Figs. 6 to 9). For the purpose of this study an attempt was made to assess the intensity of the lymphocytic infiltrate and follicular reactions by grades from 0 to 4 plus.

A 4 plus reaction in regard to lymphocytic infiltrate is characterized by a dense and diffuse accumulation of lymphocytes in and around the primary tumor. It should be emphasized that this reaction is essentially mononuclear and is not associated with a polymorphonuclear response or a fibroblastic reaction. The 4 plus lymph follicular reaction is characterized by prominent follicles in or near the primary tumor as well as in the deeper tissues of the stomach wall. Intermediate intensities of such change were assessed in relation to the two extremes of the scale. It should also be mentioned that we have arbitrarily employed the greatest intensity of reaction observed in a particular case for such grading. This tends to make whatever errors might occur unidirectional and more constant in all cases.

RESULTS

Lymph node structure. Sinusoids.—The regional lymph nodes in the death series of gastric cancer cases showed only a 7 per cent incidence of sinus histiocytosis equal to or greater than 2 plus. In contrast to the findings in the lymph nodes in the death series were the observations made on the nodes from the long survival cases. As indicated in Table I, sinus histiocytosis equal to or greater than 2 plus was found in the nodes of 30 per cent of this latter group. A statistical comparison of the incidence of the various degrees of sinus histiocytosis in the death and the 5 year cure series was made by the chi square method of testing. The probability that the observed differences would have occurred by chance was found to be less than 1 in 100. It is noteworthy that of the 15 patients with sinus histiocytosis equal to or greater than 2 plus, all of whom survived for long periods, metastases to the regional nodes were found in 5 cases.

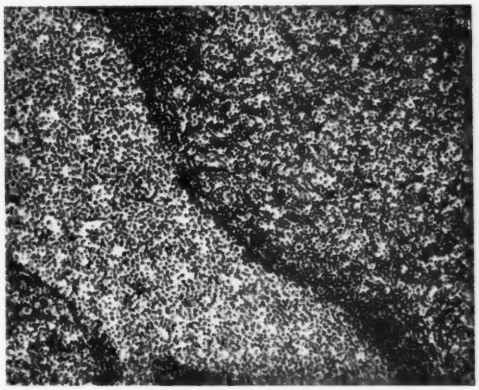

Fig. 3. Regional lymph node. Marked follicular hyperplasia showing coalescence of follicles. Note also the reticuloendotheliosis of the pulp. ×68.

These findings would be consistent with our observations on breast cancer patients which indicated that the occurrence of sinus histiocytosis of the regional lymph nodes presages a good survival and is of greater prognostic significance than the absence of regional lymph node metastases.

Follicular hyperplasia in regional lymph nodes.—In our previous study of the regional lymph nodes of breast cancer cases we noted that there appeared to be a tendency for a

TABLE II.—PER CENT INCIDENCE OF THE DEGREE OF LYMPH FOLLICULAR REACTION IN REGIONAL NODES IN GASTRIC CARCINOMA

Degree of follicular reaction	Per cent dead within 3 years (66 cases)	Per cent 5 year cures (48 cases)
0	51	11
+1	17	11
+2	25	34
+3	2	23
+4	6	21
Mean	0.95	2.34

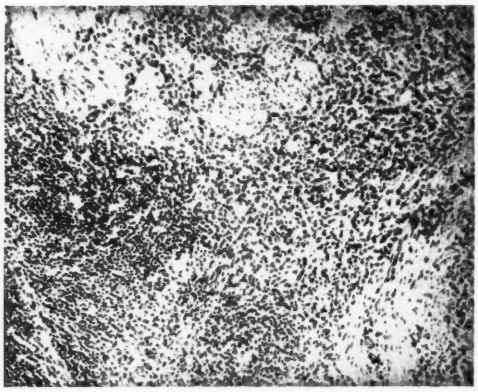

Fig. 4. Gastric wall showing marked lymphocytic infiltrate in muscularis. ×68.

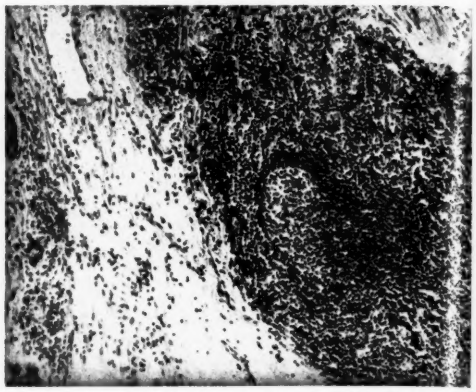

Fig. 5. Gastric wall showing area of moderate degree of follicular metaplasia and infiltrate in submucosa. ×68.

follicular hyperplasia to be associated with significant degrees of sinus histiocytosis and to occur more frequently in cases of longer survival periods. In the present study this association was also noted as indicated in Table II. It is apparent from these data that in those patients with gastric carcinoma having good survival periods the incidence of marked follicular hyperplasia (3 and 4 plus) of the regional nodes is far greater than in those dying in less than 3 years.

It should be noted, however, that good survivals were frequently found without such changes in the regional nodes. It was therefore important to study the primary tumor in the hope of determining what features were associated with those patients who experienced prolonged survivals despite a lack of reactivity of the regional nodes.

Primary tumor. Examination of the gross growth patterns of the primary tumors comprising the death series and the selected cases of long survivals revealed the presence of diverse types of structure in both groups. These were classified according to the method of Stout and included: superficial spreading cancers, fungating growths, linitis plastica, ulcer cancer, penetrating, and mixed types of growths. In Table III we have listed the percentage of incidence of these various types of gastric carcinoma as found in the two series. It will be noted that the most marked difference in the two series was in regard to the infrequency of superficial spreading growths in the death group. Despite the apparently more favorable prognosis associated with the superficial spreading type of lesion it should be mentioned that Harvey and associates reported a 54 per cent survival associated with gastric carcinomas of this type. Thus, the finding of such a growth pattern by no means implies an absolute factor prognosticating a 5 year survival in individual cases.

TABLE III. — PER CENT INCIDENCE OF VARIOUS TUMOR TYPES IN GASTRIC CARCINOMA

Tumor type	Per cent 5 year cures	Per cent dead in less than 3 years
Linitis plastica	2	8
Ulcer cancer	16	52
Fungating	32	24
No specific type	28	12
Penetrating	4	2
Superficial spreading	26	2

In Table IV we have listed some of the pertinent findings in those patients known to have long survivals. It will be noted that the most frequent finding common to these cases was the occurrence of a prominent lymphocytic reaction in the primary tumor. This reaction was in the form of a diffuse lymphocytic infiltration and lymph follicles in and around the primary tumor. In Table V we have compared the percentage of incidence of the degree of such stromal changes in the

TABLE IV.—CLINICAL AND PATHOLOGIC FINDINGS IN CASES OF GASTRIC CANCER WITH LONG SURVIVALS

Case	Sex	Age	Primary tumor		Lymph node		Years post-op.	Result
			Infil-tr.	Foll.	S.H.	F.H.		
P& 5565	M	50	2	1	4	4	23	*Died of gastric cancer
P& 90200	F	64	1	2	0	4	6	N.E.D.
P& 83757	M	46	3	3	?	?	7	N.E.D.
P& 77971	M	71	4	2	0	0	9	N.E.D.
P& 78949	M	51	2	3	0	2	12	N.E.D.
P& 78307	F	52	1	0	3	4	29	N.E.D.
P& 4656	M	50	4	4	0	2	10	N.E.D.
P& 2150	M	57	4	4	0	3	8	*N.E.D.
P& 9158	F	43	1	3	?	?	15	N.E.D.
FF 108	M	50	4	4	?	?	13	Died with cancer
P& 1960	M	45	0	0	0	2	8	Died cardiac failure, nephritis
P& 349	M	61	3	3	1	3	8	N.E.D.
P& 774	M	52	2	2	1	4	8	*N.E.D.
P& 2241	M	55	2	3	0	2	8	N.E.D.
P& 588	F	43	3	4	0	3	15	*Died-CVD
P& 814	F	60	1	3	0	2	7	N.E.D.
FFA 00	F	50	2	3	0	2	13	Died of gastric cancer
P& 3288	M	52	2	2	3	3	10	*N.E.D.
P& 81753	M	52	3	3	2	0	6	N.E.D.
P& 60354	M	61	2	2	0	1	12	N.E.D.
P& 61321	M	53	2	2	0	0	13	N.E.D.
P& 62163	M	34	4	4	0	1	11	N.E.D.
P& 70697	M	42	3	3	2	2	10	*N.E.D.
P& 81425	M	68	3	4	0	4	8	N.E.D.
P& 86477	M	48	1	2	3	2	9	N.E.D.
P&S 51049	F	63	1	2	0	1	8	*Died, cause unknown
P&S 75042	M	65	4	4	0	4	10	N.E.D.
P&S 52570	M	68	2	3	0	2	10	*Died—hip fracture
P&S 89782	F	69	2	0	1	4	6	N.E.D.
FFA 3588	M	75	3	4	?	?	5	N.E.D. Excisional biopsy only
P&S 86099	M	34	3	4	3	3	9	N.E.D.
P&S 68618	M	37	3	4	0	4	12	*N.E.D.
P&S 24486	M	37	3	3	?	?	20	N.E.D.
P&S 70182	F	39	2	2	2	3	12	*N.E.D.
P&S 78473	F	47	1	4	0	3	10	*N.E.D.

TABLE IV.—CLINICAL AND PATHOLOGIC FINDINGS IN CASES OF GASTRIC CANCER WITH LONG SURVIVALS—CONCLUDED

Case	Sex	Age	Primary tumor		Lymph node		Years post-op.	Result
			Infil-tr.	Foll.	S.H.	F.H.		
P&S 82998	F	55	2	2	3	1	8	*N.E.D.
P&S 50483	F	66	2	0	0	0	17	*N.E.D.
FFA 3895	F	52	4	4	?	?	7	N.E.D.
P&S 88046	M	54	2	4	0	2	7	*N.E.D.
P&S 78949	M	52	2	3	2	2	9	N.E.D.
FFA 4447	F	46	1	0	2	3	5	*N.E.D. 6/53
P&S 77479	M	49	3	3	0	4	13	*N.E.D.
P&S 15153	M	47	2	2	2	4	23	Died—CVD
FFA 4072	F	73	0	0	0	0	5	N.E.D. 6/53
P&S 27516	F	55	1	0	2	2	20	Died—CVD
P&S 87959	M	69	2	2	1	2	7	*N.E.D.
P&S 49008	M	48	4	4	0	1	15	Died of gastric cancer
P&S 78193	M	65	3	3	0	3	9	*N.E.D.
P&S 78516	M	46	1	2	2	3	9	N.E.D.
FFA 3492	M	55	4	3	0	2	5	N.E.D.
P&S 25909	M	59	1	3	0	3	22	Died—CVD
P&S 62199	F	61	1	0	0	2	14	N.E.D.
P&S 65783	F	68	3	2	0	2	13	N.E.D.
P&S 421	F	34	0	1	3	3	6	N.E.D.

*Metastases to regional nodes
?—no nodes removed
N.E.D.—No evidence disease
P&S—Presbyterian Hospital
FFA—Flower and Fifth Avenue Hospital
CVD—Cardiovascular disease

death series with that of the long survival series. It is evident that such stromal changes were rarely observed except in cases of long survivals. Statistical comparison of these two series by the chi square method of testing indicates that the probability that they are from the same general population is less than 1 in 1,000

In Table VI we have indicated the percentage of incidence of the degree of sinus histiocytosis of the regional nodes and the lymph follicular reaction in the primary tumor. These data indicate that there is no direct relationship between the intensity of the sinus histiocytosis of the nodes and the follicular reaction in the tumor. They further demonstrate that in 90 per cent of the cases

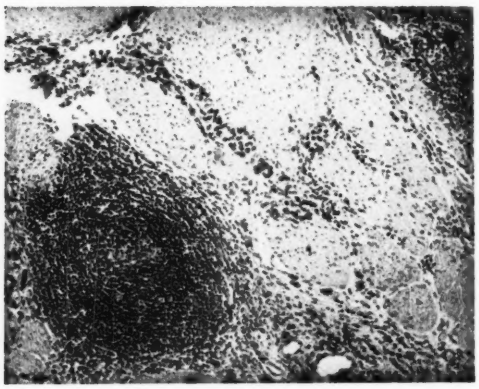

Fig. 6. Gastric wall showing focal area of follicular metaplasia without infiltrate in muscularis. Note infiltrating tumor cells. ×68.

of long survival there was at least a 2 plus reaction in regard to sinus histiocytosis or lymph follicular reaction or both. In contrast, such findings were not commonly observed in those patients known to have succumbed to the disease in less than 3 years.

In Table VII we have indicated the per cent distribution of the intensity of the lymphocytic infiltrate in the primary tumor and the sinus histiocytosis of the regional nodes in the two series. It is readily apparent that the distribution of values is strikingly different in those patients known dead of carcinoma in less than 3 years as compared with those surviving 5 years or longer postoperatively. In the former group the degree of sinus histiocytosis of the regional nodes or the lymphocytic infiltrate in the primary tumor was less than 2 plus in 93 per cent of the cases. In contrast, sinus histiocytosis or lymphocytic infiltrate of 2 plus or greater was observed in 84 per cent of the cases of prolonged survival. In short, in 89 per cent of the combined cases these criteria would have indicated a differentiation between those patients who would have survived 5 years and those who died in less than 3 years.

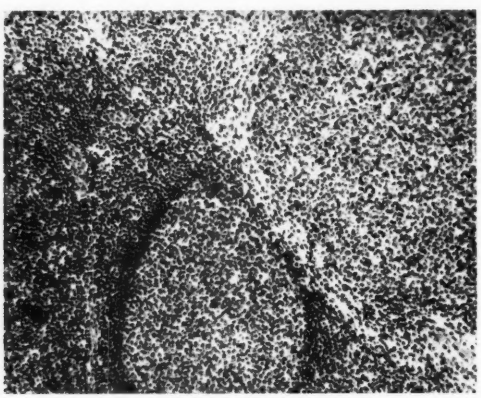

Fig. 7. Gastric wall showing marked follicular metaplasia in submucosa adjacent to tumor area. ×68.

It should also be noted that in 17 cases of the 5 year cure group regional metastases were already present at the time of surgery. Of these 17 cases all but 1 had sinus histiocytosis or a lymphoid reaction in the primary tumor of 2 plus or greater.

In 11 of the patients who succumbed in less than 3 years no regional metastases were found. Of this group, 8 had less than 2 plus sinus histiocytosis and lymphocytic reaction in the primary tumor. Thus the survival in individual cases in both groups appears to be more closely correlated with the degree of sinus histiocytosis of the regional nodes and lymphocytic reactivity of the stroma of the primary tumor than it is with the presence or absence of regional metastases.

Age of the patient. Evaluation of the age of the patients in both series revealed no significant difference between the two either in regard to the distribution of values or the mean. Thus the mean value in the 5 year cure group was 54 years while in the death group the mean was 57 years. This is consistent with the findings of others.

Preoperative delay. In common with other investigators we were unable to obtain any evidence to indicate that patients with longer survivals had a shorter delay between the time of initial symptomatology and therapeutic intervention. If anything, the contrary was the case. This latter finding has also been commented on previously by others.

DISCUSSION

The data presented indicate that those cases of gastric carcinoma with 5 year cures are characterized by the occurrence of sinus

histiocytosis of the regional nodes and/or a lymphocytic reaction in the primary tumor. In contrast, those cases of patients dying of the disease in less than 3 years are characterized by the absence of such findings.

In an attempt to evaluate more adequately the prognostic significance of varying degrees of such change we have further analyzed the data presented in Tables VI and VII. For this purpose we have combined the 5 year cure and the death series (114 cases in which the primary tumor and regional lymph nodes were available for study) and determined the number of cases of living and dead as found in each of the subdivisions of the tabulation determined by the different degrees of sinus histiocytosis and lymphocytic reaction, viz., for 48 patients having a 0 grading for sinus histiocytosis and lymphocytic infiltrate only 2 survived 5 years or longer. At the opposite borders of the square (Table VII) there were 8 patients having a 4 plus sinus histiocytosis and/or a 4 plus lymphocytic infiltrate in the primary tumor. All of these patients are known to have survived 5 years or longer. In Figure 10 we have indicated the percentage of patients surviving 5 years according to this type of grouping. It is apparent that there is a well defined linear relationship between the percentage of survival and the combined intensity of the sinus histiocytosis of the regional nodes and the lymphocytic reaction of the primary tumor.

It should be noted that this relationship obtains without any consideration of such factors as the age of the patient, type of growth, or the presence or absence of lymph node metastases. In order to test the validity of these observations further we have calculated the expected survivals based on the incidence of cases with and without regional metastases by utilizing values cited in the literature. According to statements in the literature the 5 year survival in operable gastric carcinoma is approximately 60 per cent in those cases without regional node metastases and 20 per cent in those with regional node metastases at the time of surgery. Of the 43 cases having 0-0 grading for sinus histiocytosis and lymphocytic infiltrate respectively, 8 were without demonstrable lymph node metastases at the time of surgery. The expected survival would thus be 35 cases with metastases times 0.20, plus 8 cases without metastases times 0.60 or 11.8 cases. The expected per cent survival would be 11.8/43 times 100 or 27 per cent. Actually, however, only 2 patients survived 5 years (5 per cent). The probability that such a difference would be due to chance sampling from similar populations was found to be less than 1 in 100 as judged by the chi square method of testing. In those patients having high degrees (3 and 4 plus) of sinus histiocytosis and/or lymphocytic infiltrate we found that 23 of 24 (96 per cent) survived 5 years. The calculated expected prolonged survival on the basis

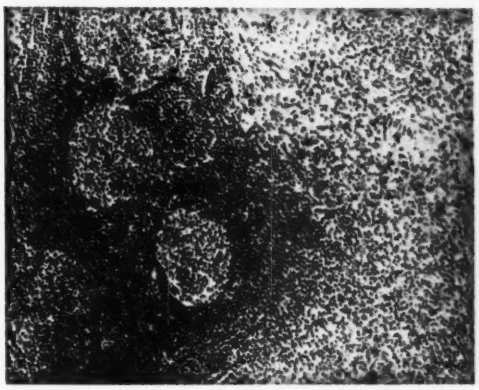

Fig. 8. Gastric wall. Lymphocytic infiltrate and follicular metaplasia in muscularis. ×68.

Fig. 9. Gastric wall. Moderate follicular prominence in adjacent uninvolved mucosa. ×68.

TABLE V.—PER CENT INCIDENCE OF LYMPHOCYTIC REACTIONS IN GASTRIC CARCINOMA

Degree of lymphatic reactions	Dead within 3 years		5 year cures	
	Follicular	Infiltrating	Follicular	Infiltrating
0	68	86	15	6
+1	15	12	4	22
+2	12	2	26	32
+3	5	—	28	24
+4	—	—	28	17
Mean	0.53	0.15	2.50	2.24

of the presence or absence of regional node metastases would only have been 11.6 cases or 48 per cent. This difference is highly significant as judged by a chi square value of 11.2 which corresponds to a P value of less than 1 in 1,000.

At the time of initiating these studies we were unaware of previous reports on the prognostic significance of lymphocytic infiltration in gastric carcinoma. However, in reviewing the literature we found that in 1921 MacCarty and Mahle (5) reported that the duration of postoperative survival in stomach carcinoma was appreciably better in those cases which showed a lymphocytic infiltrate in the tumor as compared to those without such findings. They also noted that lymphoid infiltration was not correlated with the absence of regional glandular involvement, if anything the reverse was true. In general, it appeared from their study that survival was more closely related to the degrees of lymphoid infiltrate in the tumor than to the presence or absence of lymph node metastases or the degree of differentiation of the primary tumor.

Subsequently, MacCarty (4) studied the microscopic features of cancer of stomach, breast, and rectum in an attempt to relate structure to survival. He concluded that the occurrence of lymphocytic infiltration, fibrosis, stromal hyalinization, and cellular differentiation of the primary tumor were significantly correlated with increased postoperative survivals. Our findings are certainly consistent with the thesis that the occurrence of lymphocytic infiltrate and lymph follicular metaplasia in gastric carcinoma is a decidedly favorable prognostic sign. We are at a loss to understand why this concept suggested more than 30 years ago has dropped from usage.

It is interesting to note that the occurrence of lymphoid metaplasia in carcinomas of other sites may also serve as a favorable sign. Thus, Moore and Foote called attention to the unusually favorable prognosis associated with

TABLE VI.—DEGREE OF FOLLICULAR METAPLASIA AND SINUS HISTIOCYTOSIS IN GASTRIC CARCINOMA CASES

Degree of sinus histiocytosis	Primary tumor—follicular metaplasia				
	0	1	2	3	4
	Dead within 3 years				
0	52	11	11	2	—
+1	12	3	2	3	—
+2	2	3	2	3	—
+3	2	—	—	—	—
+4	—	—	—	—	—
	5 year cures				
0	8	—	13	17	23
+1	2	—	4	2	—
+2	4	—	6	6	—
+3	2	2	6	—	2
+4	—	2	—	—	—

TABLE VII.—DEGREE OF LYMPHOCYTIC INFILTRATE AND SINUS HISTIOCYTOSIS IN GASTRIC CARCINOMA CASES

Degree of sinus histiocytosis	Primary tumor—infiltrate				
	0	1	2	3	4
	Dead within 3 years				
0	63	9	—	—	—
+1	20	2	2	—	—
+2	3	2	—	—	—
+3	2	—	—	—	—
+4	—	—	—	—	—
	5 year cures				
0	2	14	16	12	14
+1	—	—	6	2	—
+2	—	6	6	4	—
+3	2	4	4	4	—
+4	—	—	2	—	—

th presence of lymphoid infiltrate and lymph follicle formation in medullary carcinomas of th breast. In our studies we have had the opportunity of following 3 patients with breast carcinoma who are apparently free of disease 5, 8, and 10 years postoperatively despite highly anaplastic infiltrating primary lesions and no evidence of sinus histiocytosis of the regional nodes. These cases all showed marked lymphoid metaplasia in or near the primary tumor. Of particular interest is the patient now 10 years postoperative without evidence of disease. In this instance only simple excision of the breast mass and regional radiation therapy were performed. Despite this unconventional therapy for an infiltrating poorly differentiated carcinoma of the breast the patient is apparently free of disease.

The present data are also of importance in regard to the relative significance of the intrinsic biologic features of cancer cases as compared with attempts at ultraradical surgery in influencing survival. In none of the patients with long survival periods was total gastrectomy performed, in 7 of them the resection failed to include any regional nodes, and in 1 case only an excisional biopsy was performed. Also of interest is the observation that despite prolonged survivals 4 of these patients died of, or with, residual carcinoma 15, 13, 13, and 23 years after operation. These findings would lend little support to the thesis of more radical surgery as a potential means of curing more cases of cancer of the stomach. Rather, these data are in accord with the concept that biologic tumor-host relationships determine the clinical course of many, if not most, cancer cases.

The observation that almost 90 per cent of the gastric cancer patients with good survival periods differed from those with poor survival periods in regard to sinus histiocytosis of the regional nodes and lymphoid metaplasia in the primary tumor suggests that such changes might be a visualization of critical biologic variables which influence the survival in individual cancer cases. Such changes appear to be of greater prognostic significance than the age of the patient, presence or absence of regional metastases, delay before surgical intervention, or the growth pattern of the tumor.

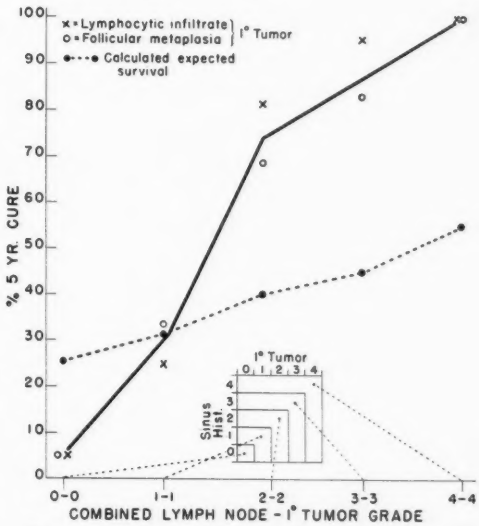

Fig. 10. Relationship between percentage of 5 year cures and degree of sinus histiocytosis of regional nodes and lymphocytic reaction in primary tumor.

Certainly the present findings emphasize the complexity of factors determining survival in individual cancer patients. They further indicate the need for continued study of such variables, particularly in regard to the tumor-host interrelationship. It is hoped that continued attention to this aspect of the cancer problem will aid in a better understanding of the biologic behavior of cancer.

SUMMARY

A comparison was made of the gross and microscopic features of two series of gastric carcinoma cases. One series consisted of 66 patients known to have died within 3 years postoperatively. The other included 54 patients who survived 5 years or longer postoperatively. The data obtained indicated that longer survival in cases of gastric carcinoma was associated with the presence of a lymphocytic reaction in the stroma of the primary tumor and/or sinus histiocytosis of the regional lymph nodes. These features were more critically related to survival than the age or sex of the patient, the preoperative delay, the gross or microscopic growth pat-

tern of the tumor, or the presence or absence of regional lymph node metastases at the time of surgery.

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THE APPLICATION OF PELVIC VENOGRAPHY TO DIAGNOSTIC PROBLEMS ASSOCIATED WITH CANCER OF THE FEMALE GENITAL TRACT

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VENOGRAPHY is a well established method for the diagnosis of pathologic conditions of the venous system and its historical aspects have recently been reviewed by Hellsten. Most of the veins of the human body, especially those of the lower extremities have been investigated by this method, but the veins of the pelvis have received relatively little attention. Barron applied the method to the study of the collateral circulation of the pelvic and spinal venous system in anatomic preparations. Farinās attempted to localize obstructions of the inferior vena cava and noted that the initial portions of the internal iliac veins could also be demonstrated in vivo by the application of an inflated rubber bag to the epigastric region. Ducuing, Guilhem, Marques, Baux and Paille (2, 3) reported that the deep veins of the pelvis can be outlined in vivo by injection of radio-opaque material into the saphenous vein, into the dorsal vein of the penis, or by using the transosseous route.

The purpose of the present investigations was to apply the procedure to the following significant clinical problems: (1) a differentiation between lymphatic and venous occlusion as a cause of edema of the lower extremities; (2) a means of determining the point of union of external and internal iliac veins for the purpose of localizing pelvic lymph node areas when radiotherapy is contemplated; (3) a demonstration of the possible collateral circulatory systems of the pelvis; (4) a correlation of in vivo venographic findings with observations made at autopsy.

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THE ANATOMY OF THE PELVIC VENOUS SYSTEM

A system of paired venous channels drains blood from specific regions of the true pelvis into the hypogastric veins which combine with the external iliac veins to form the common iliac veins. The point of union, that is, the beginning of the common iliac veins, is at the brim of the pelvis opposite the sacroiliac joints. The right and left common iliac veins terminate by forming the inferior vena cava at the upper border of the fifth lumbar vertebra. The left runs medial to the corresponding artery, then crosses the midline by passing obliquely underneath the right common iliac artery, over the promontory of the sacrum and the fifth lumbar vertebra. It terminates by joining the right common iliac vein at the level of the upper right border of the fifth lumbar vertebra. The right common iliac vein is shorter and has a more longitudinal course than its fellow on the left; the corresponding artery is at first anterior and then anteromedial to it. Its tributaries are the external iliac, the internal iliac, the venae comitantes of the median sacral artery (which communicate with the anterior sacral plexus), and the iliolumbar veins which sometimes drain into the internal iliac veins.

The internal iliac veins begin at the upper border of the great sciatic foramina and end at the sacroiliac articulations. They lie posterior to the corresponding arteries and receive two major types of tributaries (1) parietal: the superior gluteal, the lateral sacral, the obturator, the inferior gluteal, and the internal pudendal vein; (2) visceral: the uterine, the vesical, and the hemorrhoidal plexus.

The external iliac veins begin at the inguinal ligament as a continuation of the femoral veins. They lie at first medial, then poste-

Fig. 1. Patient P.P. Venogram performed 4 weeks after a radical vulvectomy and bilateral lymphadenectomy. The right pelvic veins are patent and a retrograde flow into the internal iliac vein is produced by temporary, partial obstruction of the inferior vena cava with an inflated rubber bag applied to the abdomen. The shadows in the center of the pelvis represent calcified fibromyoma of the uterus.

rior to the corresponding artery and end at the sacroiliac articulation. Their tributaries are: the deep circumflex iliac, the inferior epigastric and pubic veins, which communicate with the obturator veins.

METHOD AND MATERIALS

Clinical material. About 40 venographic determinations were performed on a variety of patients with cancer of the female genital tract. The patients were selected at random, and the method used as an aid in the preoperative diagnosis, or as a test of the accuracy of the method to be verified at autopsy. An attempt was made to repeat these venographic determinations as indicated by the patient's clinical course. Whenever possible, a similar determination was performed at autopsy.

Method and procedure. The femoral veins are usually located with ease and can be punctured by means of a No. 18 gauge needle at a point just below the inguinal ligament. If the lower extremities are edematous, or the femoral veins found to be thrombosed, a cutdown must be performed for the purpose of cannulating the saphenous vein.

A slow infusion of normal saline is started and, after insuring that the system is free of leaks, the patient is placed upon the x-ray table and a rubber compression bag applied to the umbilical region. The bag is inflated a few minutes before the injection of the contrast medium. The plastic infusion tubing is clamped off, and the contrast medium injected into the lower portion of the infusion system. This arrangement is preferable to direct injection into the (femoral)vein because it permits the operator to perform the procedure at a safe distance from the x-ray machine.

The radio-opaque substance used throughout these investigations was neo-iopax[1] in concentrations of 50 or 75 per cent. The amount injected varied from 20 to 50 cubic centimeters on each side, at a rate of 1.5 to 2 cubic centimeters per second. For practical purposes it was found that maximal contrast and visualization of the internal iliac veins and tributaries to the external iliac veins was obtained 10 seconds after the initiation of the injection.

The only complication observed during these investigations was an occasional paravenous infiltration of the radio-opaque material. This occurred in roughly 10 per cent of all tests. Most patients in whom paravenous infiltration had occurred had additional roentgenograms taken 3 days after the tests. None of these showed residual radioopacities at the site of infiltration. In some patients the opportunity presented itself to inspect the area of infiltration at operation, at which time no untoward effects were noted.

Satisfactory roentgenograms were obtained on 14 by 17 inch films with exposures of 30 milliampere-seconds at 85 kilovolts (average) at 40 inches target film distance. In some cases serial roentgenograms were made with a camera taking 2 exposures per second.

CASE HISTORIES

In order to demonstrate the applicability of this method to a variety of situations, several clinical examples are given. These examples represent characteristic problems encountered in cancer therapy. In the following a brief history of 7 patients is presented with roentgenograms pertaining to each.

[1]Neo-iopax is the disodium salt of N-methyl-3, 5-diiodochelidamic acid, a pyridine derivative containing 51.5 per cent iodine.

CASE 1. P.P., D.H. No. 1530, a 78 year old nullipara, had an uneventful menopause at the age of 43 years. Her admission diagnosis was carcinoma of the vulva involving the lower right labium majus. In spite of therapy with radium needles, the disease persisted, which made it necessary to perform a radical vulvectomy with bilateral inguinal lymph node dissection. Her postoperative course was uneventful, with the exception of the development of edema of both legs. When ambulated, the edema increased but was slowly controlled by application of ace bandages and frequent elevation of the legs. A venogram, performed at the height of edema, is reproduced in Figure 1.

CASE 2. J.R., D.H. No. 2107, was a 57 year old multigravida whose history included a supravaginal hysterectomy at the age of 31 years. Three years prior to her present admission she had complained of swelling in the left groin. Her physician made a diagnosis of epidermoid carcinoma of the cervix on the basis of a biopsy. She was admitted to a university hospital where the lesion was treated with radium and external x-ray. Her postoperative course was satisfactory. Two years prior to her present admission, she had been treated for phlebitis of the left leg. Although discharged in improved condition, the pain in the left leg persisted, and 1 year later an indurated mass fixed to the left pelvic wall was noted during a routine follow-up examination. The patient was admitted to the Francis Delafield Hospital where, in the course of work-up, a bilateral venogram was performed. This is reproduced in Figure 2. She had a surprisingly rapid downhill course and expired without further, specific therapy.

An autopsy was performed, the essential findings of which were the presence of a large pelvic abscess, a well defined fistula between sigmoid and vagina, and complete occlusion of the left external iliac vein, produced by compression and thrombosis attributed to chronic inflammatory processes in the surrounding structures.

CASE 3. M.S., D.H. No. 2777, a 68 year old para 8, gravida 8, had had an uneventful menopause 18 years previously. Her admission diagnosis was carcinoma of the corpus uteri, stage IV, for which she had been treated by external radiation in another hospital. The significant findings during the initial physical examination were: notably dilated veins along the lateral sides of the abdomen and chest and a complete absence of edema of the lower extremities. On pelvic examination a large, firm, fixed mass was found filling the pelvic cavity completely and extending upward halfway to the umbilicus. A venogram was performed shortly after admission, which is reproduced in Figure 3. She had a rapid downhill course and died a few weeks after admission. Permission for autopsy was denied.

CASE 4. R.S., D.H. No. 2686, a 55 year old para 1, gravida 1, had had an artificial menopause at the age of 52 years, when she received radium and x-ray therapy for carcinoma of the cervix, stage III,

Fig. 2. Patient J.R. Bilateral venogram performed to determine the etiology of edema of the left lower extremity. The contrast medium was injected through the saphenous vein because the left femoral vein could not be punctured. It demonstrates a complete obstruction of the femoral and external iliac veins with formation of collateral circulatory channels via the pubic and circumflex veins. The right pelvic veins are normal.

at another hospital. On admission, she complained of low back pain and pain radiating along the right leg. Pelvic examination revealed scarring of the right parametrial region and an enlarged "right lateral" lymph node. A venogram was performed during a routine diagnostic work-up, which is reproduced in Figure 4. On the basis of a neurologic investigation and roentgenograms of the lower spine, a diagnosis of metastatic carcinoma involving the second, third, and fourth lumbar vertebrae was made.

CASE 5. R.R., D.H. No. 1689, a 48 year old para 12, gravida 12, had an admission diagnosis of carcinoma of the cervix, stage III. Following a routine work-up, the patient was subjected to an exploratory laparotomy. During an attempt to dissect a tumor mass involving the right pelvic wall, a major tributary to the hypogastric or external iliac vein was torn, which necessitated a ligature of that vessel. Her postoperative course was uneventful and remarkable in that she did not develop edema of the right lower extremity as a result of the ligation of the external iliac vein. Following complete recovery from the operation the plan of therapy was changed and she received radium and external radiation. During her convalescence a venogram was performed, which is reproduced in Figure 5.

CASE 6. D.B., D.H. No. 2183, a 34 year old nulligravida, was admitted to the hospital because of menometrorrhagia and lower abdominal pain. On

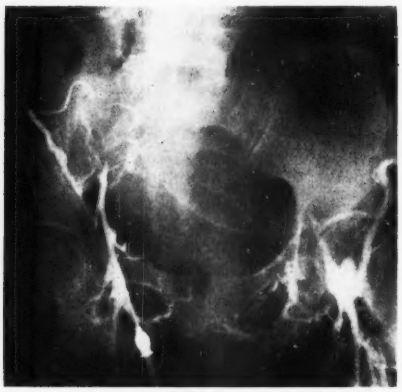


Fig. 3.

Fig. 4.

Fig. 5.

Fig. 3. Patient M.S. The contrast medium was injected through a tributary of the femoral vein. An excellent collateral circulatory channel via the circumflex veins and complete obstruction of both external iliac veins can be seen.

Fig. 4. Patient R.S. Bilateral femoral venogram produced by injection of the contrast medium into the femoral veins with temporary obstruction of the inferior vena cava. Retrograde flow into the internal iliacs was effective enough to outline clearly the venous drainage of the uterus and bladder. The ovarian vessel on the left is clearly delineated.

Fig. 5. Patient R.R. A unilateral venogram produced by injection of the contrast medium into the right femoral vein, about 2½ weeks following ligation of the right external iliac vein. The collateral circulation through the obturator and internal iliac veins into the common iliac vein and vena cava is well shown.

pelvic examination the uterus was found to be about three times normal size with a well defined subserous fibromyoma 10 to 12 centimeters in diameter. During a routine work-up for the anticipated operation, a venogram was performed which is reproduced in Figure 6. The roentgenogram showed a narrowing of the external iliac veins thought to be due to external pressure. A laparotomy was performed which confirmed the preoperative diagnosis of fibromyoma of the uterus; the veins of the pelvis were found to be compressed by the tumor. Following a total hysterectomy, the patient had an uneventful postoperative course and was discharged in good condition.

Case 7. A.A., D.H. No. 2854, a 55 year old para 3, gravida 3, could not recall the date of her last normal menstrual period. Three years prior to her present admission, a dilatation and curettage had been performed in another hospital because of postmenopausal bleeding. The diagnosis of adenocarcinoma of the corpus uteri led to radium and x-ray therapy followed by total hysterectomy and bilateral salpingo-oophorectomy. Two months before her admission an ill defined mass was noted during a pelvic examination, and the patient was referred to the Francis Delafield Hospital for further treatment. The admission examination confirmed the presence of the mass described; mild bilateral edema of the lower extremities was the only other positive physical finding. The patient complained of severe pain along the lower right extremity of approximately 3 months' duration. After routine preparation an exploratory laparotomy was performed, the mass was identified as a dermoid cyst

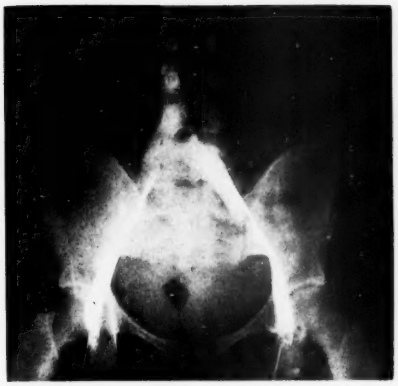
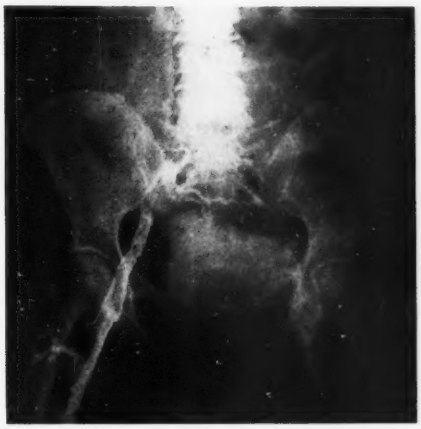


Fig. 6.

Fig. 6. Patient D.B. Bilateral femoral venogram with application of pressure to the inferior vena cava. This represents the characteristic pattern obtained with partial obstruction of the external iliac veins due to extrinsic pressure. Note the smooth narrowing and only minimal displacement of localized segments of the left external and right common iliac veins. There are no filling defects within the venous lumina.

Fig. 7. a, Patient A.A. Venogram taken to determine the patency of venous channels. The illustration shows extensive characteristic mottling and filling defects within the femoral and external iliac veins. There is complete obstruction of the common iliac vein and diversion of the flow through the internal iliac and lumbar veins. b, Venogram taken 8 weeks later. The contrast medium was injected into the femoral vein on the left and the saphenous vein on the right. There is now complete obstruction of the external and common iliac veins on the right with development of collateral circulation across the pubis. There is also obstruction of the terminal portion of the left common iliac vein, with collateral circulation through the left iliolumbar system.



a

b

Fig. 7.

and removed. Nothing else of significance was found. Two weeks following the exploratory laparotomy, a venogram was performed which is reproduced in Figure 7a. A complete obstruction of the right common iliac vein with collateral circulation through the internal iliac vein and sacral plexus was noted. A follow-up venogram 8 weeks later (Fig. 7b) showed evidence of complete obstruction of the right common iliac, external iliac, and upper part of the femoral veins as well as clearly defined collateral channels across the pubic area to the opposite femoral vein. The patient expired a few weeks after the last venogram. The autopsy revealed a recurrence of the lesion along the right psoas muscle involving the external iliac and common iliac veins with partial invasion of the wall of the inferior vena cava.

DISCUSSION

Although it would seem to be extremely difficult to develop hard and fast rules for the interpretation of venograms, an analysis of these pictures in the light of the clinical course of the patients may be instructive. A number of common factors can be observed, the existence of which is, of course, not limited to the 7 examples cited, but based on a much larger body of data.

Fig. 8. Patient L.M. A bilateral femoral venogram demonstrating smooth narrowing of external and common iliac veins and a collateral circulation via the iliolumbar veins. An exploratory laparotomy showed that the partial obstruction was due to bilateral tuberculous adenitis of the pelvic lymph nodes.

In the absence of obvious obstruction, and without external pressure on the inferior vena cava, almost always the external iliac veins, the common iliac veins, and the inferior vena cava can be outlined (Fig. 9). By the application of an inflated rubber bag to the umbilical region a normal pattern of the deep veins of the pelvis can be produced, as shown in Figure 4. Here, retrograde flow into the internal iliac, uterine vein, vesical plexus, and left ovarian vein can be outlined.

If the test is performed properly, the roentgenogram shows a clear outline of the veins. These appear very slightly distended, but are quite uniform in width and intensity of their shadows. Partial obstruction due to external pressure produces a smooth narrowing of the diameter as shown in Figure 6, where the external iliac and common iliac veins have been compressed by a large subserous fibromyoma of the uterus. In contrast to the uniformity of the shadow in Figure 6, the mottled appearance of the vessels in Figure 7a can be correlated with partial obstruction of the venous channels attributable to thrombophlebitis.

An occlusion of the external iliac vein might be expected to result in edema of the affected leg. That this is not a necessary consequence is demonstrated by Case 5, patient R.R., whose right external iliac vein had been ligated because of an operative accident. During the postoperative period, a venographic investigation (Fig. 5) was performed in order to find an explanation for the unexpected absence of this edema. At least in this particular instance, the obturator vein alone seemed to represent a more than adequate collateral channel.

Further analysis of the available material led to the observation that whenever a major vessel became obstructed by any cause whatsoever, collateral circulation developed. The characteristics of this collateral circulation appeared to be dependent upon the nature and location of the obstruction.

The application of an inflated rubber bag causes an artificial, temporary, and acute obstruction of the inferior vena cava. Under these conditions a retrograde flow may take place through the iliolumbar veins, the internal iliac veins, or both (Fig. 8). Whenever the contrast medium appeared in the iliolumbar veins, the internal iliac veins were filled, at least in part; if, on the other hand, the internal iliacs were seen, the iliolumbar system very frequently showed inadequate or no filling. The retrograde flow through the internal iliac veins, therefore, appeared to be the preferred or primary collateral channel, and only in the event of its obstruction or inadequacy, the iliolumbar route was utilized.

This finding was strikingly consistent and only 2 instances were noted in which the iliolumbar system was visualized, but the internal iliac veins were not. In both cases the explanation was found at autopsy: one showed complete obstruction of the internal iliac vessels by an ovarian mass, the other a similar obstruction by massive tuberculous adenitis.

Under particularly favorable circumstances, in which retrograde flow into the internal iliac veins is easily accomplished, a third collateral channel via the ovarian veins can usually be demonstrated. This assumes clinical significance in the event of an obstruction of the common iliac or the internal iliac vein. Since

these collateral channels function with such readiness under the acute conditions of the test, one may assume that they have an even greater significance when chronic and progressive obstruction of the major vessels is produced. This is illustrated in Figure 7b, where a partial occlusion of the left common iliac had diverted the flow through the right iliolumbar veins, an effect produced without the application of an inflated rubber bag. In the event that the obstruction occurs at a level distal to the union of external and internal iliac veins, the drainage takes place either across the pubis (Fig. 7b) or through the inferior epigastric and circumflex veins (Fig. 3). If neither of these channels remain patent, then a series of smaller vessels assumes their function.

The development of collateral channels is shown in 2 successive venograms on patient K.A. The first of these (Fig. 7a) shows a complete obstruction of the right common iliac vein due to thrombophlebitis and diversion of the blood flow through the internal iliac vein and pelvic plexus. A venogram taken 8 weeks later (Fig. 7b) shows complete obstruction of the external iliac and common iliac vein, as well as partial obstruction of the left common iliac vein with pronounced, collateral circulation across the pubis, and the iliolumbar veins on the left. The absence of a collateral channel through the left ovarian vein is easily explained by the surgical absence of the uterus and both adnexa. An autopsy performed shortly after the last venogram confirmed these findings.

Based upon these and similar examples, there exists a certain degree of correlation between the clinical symptoms of peripheral edema and the status of the pelvic venous system. In the absence of other edema-producing factors, an obstruction of one (Fig. 5) or more (Fig. 3) major vessels draining the pelvis and extremity does not cause edema if the potential collateral circulation remains intact. If the obstruction of the major vessels is associated with an inflammatory process, such as thrombophlebitis, cellulitis, and regional adenities, then, in spite of apparently adequate collateral channels (Figs. 2, 7a, and 7b), peripheral edema will be a major symptom.

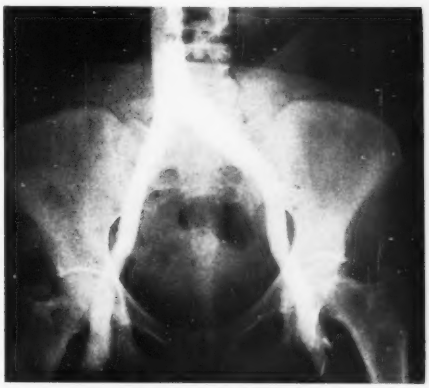


Fig. 9. Patient K.B. A routine venogram on a normal patient taken without compression of the inferior vena cava. The rubber bag seen on the abdomen was not inflated prior to injection. Note the characteristic absence of collateral circulation and lack of retrograde flow into the internal iliac veins.

An example of impaired lymphatic drainage is represented by patient P.P. This patient had a radical vulvectomy with bilateral inguinal and femoral lymphadenectomy, which, as usual, resulted in temporary, though severe edema of both lower extremities. A venogram (Fig. 1) shows an entirely normal pattern for the iliac veins with retrograde flow into the internal iliac vein. The venous return was, therefore, not impaired, and the edema could be attributed to inadequate lymphatic drainage alone.

In spite of some limitations, venographic studies of the pelvis may be of considerable significance in the prognosis and therapy of patients with cancer of the female genital tract. Initially, an accurate diagnosis is important and becomes essential for the proper evaluation of patients in advanced stages of the disease. Thus, the edema found in stages III and IV of carcinoma of the cervix may be due to lymphatic obstructions, if the inguinal lymph nodes are involved, or it may be due to the occlusion of venous channels. Chronic progressive edema, if due to the former, has an extremely poor prognosis, while the latter with or without inflammatory changes, may be amenable to surgical treatment.

Venography may further be of considerable assistance in radiation therapy, when the

exact location of the lymph node areas within the pelvis may be desirable. Of particular interest to the radiotherapist is the nest of nodes at or near the point of union of the external and internal iliac vessels, a point which does not show a constant relation to the bony landmarks of the pelvis. Although the present studies were performed on a wide variety of patients, and include far advanced cases of carcinoma, this point of union could be demonstrated in 80 per cent of them. In less advanced cases in which specific radiotherapy might be used to greatest advantage, an even higher percentage of successes can be anticipated. Any of the accepted methods of pelvimetry, including stereoscopic analyses, could be applied to this end and provide the radiotherapist with exact data for the calculation of the desired dosage. Its application to radiotherapy is obviously beyond the scope of this report.

SUMMARY AND CONCLUSIONS

A simple method for the x-ray visualization of the major pelvic veins has been described. The method has been applied to a variety of clinical problems encountered in the treatment of gynecologic cancer patients. The observations were interpreted as follows:

1. Obstruction of any of the major pelvic vessels produces a shunting of blood through collateral channels. Depending upon the nature and site of the obstruction, this shunting occurs through one or more of the following collateral channels: (1) the inferior epigastric and circumflex veins; (2) the internal iliac, uterine, and ovarian veins, or the internal spinal plexus; (3) the iliolumbar, or the lumbar spinal plexus; (4) the pubic veins; (5) the obturator vein; and (6) superficial but inadequate channels.

2. The edema of a lower extremity can be attributed to venous obstruction only in the absence of good collateral circulation. If an adequate collateral circulation can be demonstrated, the edema must be attributed to inflammatory changes or lymphatic obstruction or both.

3. Venography represents a means for the accurate localization of the point of union of external and internal iliac veins. Its reference to the bony landmarks of the pelvis should be an aid in the calculation of the dosage if radiation therapy is contemplated.

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THE EFFECTS OF URETHROCYSTOPEXY FOR STRESS INCONTINENCE

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URETHROCYSTOPEXY offers a relatively simple alternative to urethral sling operations in the treatment of stress incontinence not ured by vaginal plastic procedures, and it has chieved a certain degree of popularity since he publication of favorable reports on its use y Williams, Marshall, Marchetti, and Krantz, halmers, and others. The method is not new, owever, for similar procedures were described nd utilized by Bonney in 1923 and by Furniss 1925. Reports published in recent years are ased on a short period of follow-up of cases, nd it is not yet possible to assess the ultimate alue of this type of operation. This comunication is concerned primarily with the efcts of urethrocystopexy on the anatomy of he urinary apparatus as shown by cystoethrography, and represents a continuation studies previously reported by Roberts (8, and Jeffcoate and Roberts (4, 5).

MATERIAL

Cystourethrography was carried out after some form of urethrocystopexy for stress incontinence in 24 women. In 15 cases comparable observations were also made before operation. All but 2 women had previously been operated on unsuccessfully by the vaginal route; 12 once, 4 twice, 4 thrice, and 2 four times. Urethrocystopexy was combined with abdominal hysterectomy twice and with Gilliam's ventrosuspension operation once.

The period of follow-up varied from a few weeks to 18 months. At the time of examination 19 women were relieved of their symptoms while incontinence persisted or recurred in the remaining 5. These results are not to be regarded as an indication of the value of the operation because the material is in some respects selected. Two of the failures were obtained by deliberate search, the clinical details and roentgenograms being provided in one case by Mr. J. H. Peel while the other case was referred by Mr. H. V. Corbett. Unselected material comprises 22 cases with 3 failures to date.

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CYSTOURETHROGRAPHY

Technique. Since the original description of the method used for lateral cystourethrography the technique has been modified and developed. High speed intensifying screen film casettes have made it possible to increase the tube-film distance. This results in a better lateral projection of the pelvis with improved definition, and at the same time reduces the possibility of excessive skin irradiation. The exposure now used is as follows: 85 to 90 kilovolts at 200 milliamperes for 2 to 2.5 seconds at a tube-film distance of 36 to 42 inches. Soft tissue scatter is reduced by coning down to a minimum and by using a 1 millimeter aluminum filter on the tube where necessary.

Results. Successful cases.—Comparison of the appearances before and after operation was possible in 12 out of the 19 cases so far classified as successful. Obliteration of the posterior urethrovesical angle at ease or on straining was a feature of all the preoperative studies, and was accompanied by funneling or leakage of fluid into the upper urethra in 7 cases.

The most constant finding after a successful operation was restoration of the posterior urethrovesical angle; it was present in all except 1 of the 19 cases (Figs. 1, 2, 3, 4, 5). Funneling of the urethrovesical junction was not invariably corrected. It persisted in 2 women, and in another 3 women, on whom roentgenograms were made before and after operation,

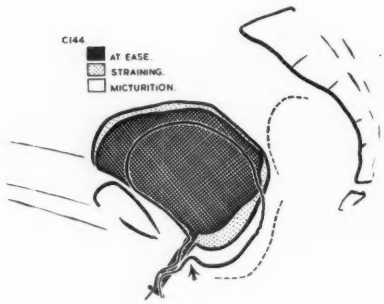
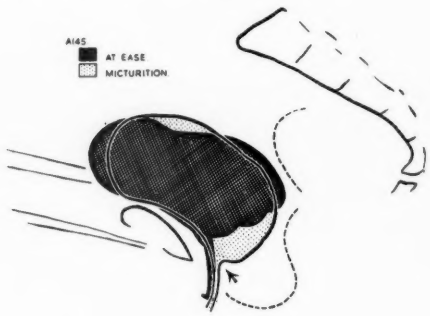


Fig. 1.



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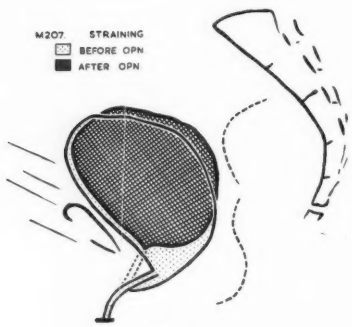

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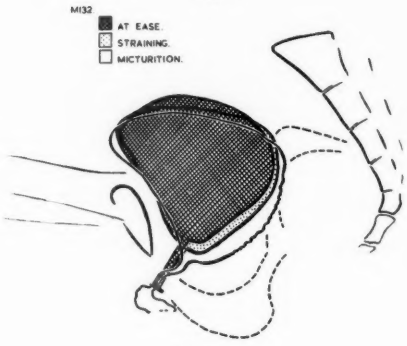

Fig. 4.

Fig. 1. Superimposed tracings of roentgenograms taken 9 months after a successful Marchetti operation. The posterior urethrovesical angle is restored and remains to some extent even during micturition (arrow). Note absence of elevation of the urethrovesical junction.

Fig. 2. Superimposed tracings of roentgenograms 12 months after a successful Marchetti operation. The urethra and bladder base are elevated to a normal position and the posterior urethrovesical angle restored. The latter is probably the more significant feature.

Fig. 3. Superimposed tracings of cystourethrograms taken before and 3 weeks after a successful Marchetti operation. (Patient straining.) The posterior urethrovesical angle is restored but slight funneling of the urethrovesical junction persists. The latter does not seem to affect the end result.

Fig. 4. Superimposed tracings of roentgenograms taken 3 weeks after a successful Williams type operation. The posterior angle is restored and persists even during micturition.

this deformity appeared to have been produced by urethrocystopexy (Fig. 5a). The funneling which was first found after operation involved only the anterior lip of the internal urethral meatus and was presumably the result of sutures being so placed that they drew the anterior part of the urethrovesical junction forward without, at the same time, bringing forward the whole area of bladder and urethra. In other words, the laterally placed sutures were relatively inadequate, and those placed directly in the middle line might have been better omitted.

A successful operation usually resulted in some uplift of the bladder base but this was not a striking feature. The urethrovesical junction was raised to the normal position in 2 women and to a higher position in 4. Prolonged postoperative retention of urine, followed by a phase of inability to empty the bladder completely, was a feature of these 4 cases. Moderate difficulty in micturition, especially in commencing the act, was noted in 3 further cases.

Difficulty in micturition occurred especially when the urethrovesical junction was unduly

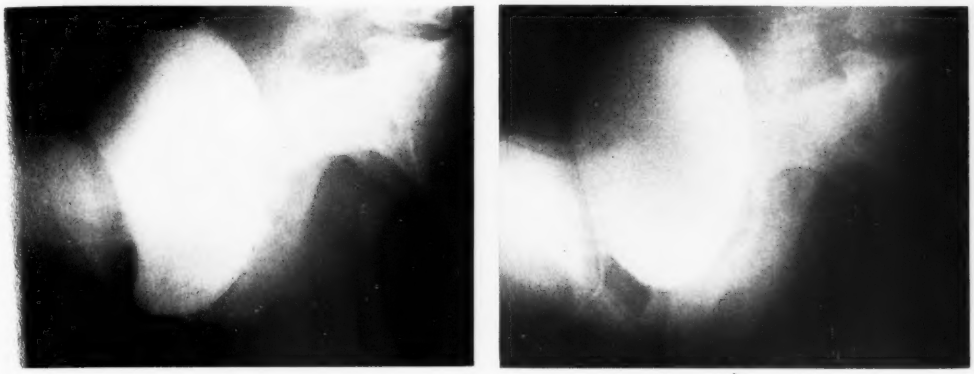

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Fig. 5. Roentgenograms 3 weeks after a successful Marshetti operation. a, Patient straining. Excessive elevation of the urethrovesical junction with funneling of its anterior margin. Deep bladder pouch below and behind the urethrovesical junction. b, During micturition. Angulation of the urethra at the urethrovesical junction with narrowing of the lumen was responsible for considerable difficulty in starting micturition.

vated and immobilized, and appeared to be a result of extreme angulation of the urethra at the urethrovesical junction and narrowing of the urinary stream (Fig. 5). An exaggerated lift may also have the effect of leaving a pouch of bladder at the back which is never completely emptied. Undue fixation of the bladder base interferes with initiation of micturition because it prevents the normal descent which acts as a trigger to set off a contraction of the detrusor muscle. If this reflex is absent the patient must await spontaneous detrusor contraction precipitated by considerable distention, or even overdistention, states which can ultimately lead to partial or complete bladder anesthesia.

It should be noted that after a successful operation the posterior urethrovesical angle does not disappear completely during micturition, or there is a suggestion of a kink in the upper urethra (Figs. 1, 2, 4, 5b, and 12). The appearance is rather similar to that seen after a successful Aldridge sling operation. This feature, however, does not seem to interfere materially with emptying of the bladder.

Failures.—Five women continued to complain of stress incontinence after the operation. One of these was referred by another surgeon merely for cystourethrography. The x-ray films showed restoration of the normal anatomy of the urethrovesical junction but also revealed that during micturition there was a leak of radio-opaque fluid from the urethra into the vagina (Fig. 6). She had in fact a urethrovaginal fistula dating from anterior colporrhaphy. During micturition the vagina filled with urine and this then trickled away during movement for some time afterward. The diagnosis was missed on clinical examination and a Marshall-Marchetti-Krantz operation was carried out for what was wrongly supposed to be stress incontinence. When this procedure too failed, cystourethrography revealed the true diagnosis which was then confirmed by more careful analysis of the symptoms.

The remaining 4 women (3 of whom were studied roentgenologically before operation) continued to suffer from true stress incontinence, this symptom returning within 3 weeks of operation in 2 cases and at 2 and 6 months after operation in the other 2. Cystourethrography showed the typical features of stress incontinence with loss of the posterior urethrovesical angle in 3 of the cases (Figs. 7, 8, and 9). Serial studies showed that while the operation was still successful the normal anatomy of the urethrovesical junction was restored. The return of incontinence, however, was associated with gradual or sudden loss of the posterior angle (Figs. 8 and 9).

In the fourth of this group of failed cases, cystourethrography indicated that the posterior urethrovesical angle had been restored by operation, but there was still funneling of

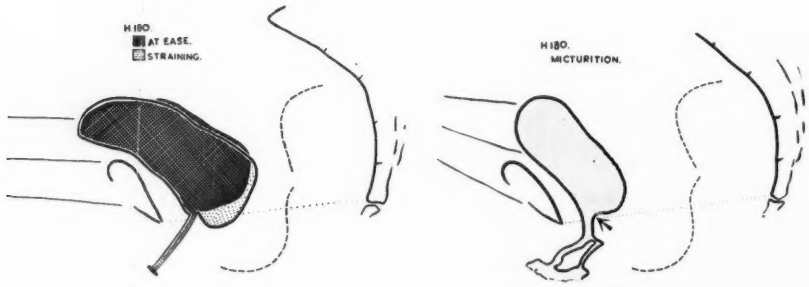

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Fig. 6. Tracings of cystourethrograms obtained 12 months after an apparently unsuccessful Marchetti operation. a, The appearances with the patient at ease and straining show a good anatomic result with restoration of the posterior urethrovesical angle. b, During micturition. Leakage of fluid from the middle of the urethra into the vagina through a previously undetected fistula.

the urethrovesical junction and leakage of fluid into the urethra on straining (Fig. 10).

Failure of the posterior urethrovesical angle to fall away or kinking of the upper urethra during micturition, which is a feature of a successful urethrocystopexy, is not seen when the operation fails.

Another recent case, not included in this series, is worthy of mention. After a series of operations—vaginal repair twice, fascial sling, Marchetti urethrocystopexy, and Mulvany vesicourethrolysis, carried out in that order—the patient was referred for investigation of severe stress incontinence which had never been improved for longer than 3 months by any of these procedures. Investigation did not reveal any neurologic lesion to account for her symptoms and cystourethrography showed a surprisingly normal appearance of the bladder and urethra, although leakage of fluid occurred around the catheter during straining (Fig. 11). In this case there was no anatomic defect demonstrable roentgenologically and the explanation of the persisting incontinence can only be presumed. On clinical examination it was notable that the lower vaginal wall and adjacent tissues were extremely rigid and fixed by scar tissue and it may well be that in this case the muscles around the urethra and internal meatus were largely replaced by fibrous tissue with resulting loss of the normal elasticity and tone which go to make up the "urethral resistance." The urethra was, in fact, converted to a tube with walls so rigid that they cannot come into firm apposition.

THE EFFECT OF DIFFERENT TECHNIQUES

Marshall-Marchetti-Krantz technique. This technique was used in 19 cases and although different surgeons introduced minor modifications the essential steps in the operation were the same in all cases. Catgut sutures were used to stitch the paraurethral tissues, the urethrovesical junction, and an area of bladder above this, to the back of pubic bones and to the fascia of the abdominal wall just above the symphysis pubis. One of these operations was carried out in error for urinary incontinence which subsequently proved to be caused by a vesicovaginal fistula (*vide supra*). Among the remaining cases there were 2 failures. In these incontinence recurred suddenly, and without obvious cause, several months after operation and was as severe as before operation.

All the cases of difficulty of micturition associated with excessive elevation of the urethrovesical junction occurred when this technique was used. One woman had always to assume the erect posture to empty the bladder even 18 months after operation.

After this operation the posterior urethrovesical angle was restored in all except 1 successful case, and remained so except in the 2 women who suffered a relapse of symptoms.

Williams technique. The Williams technique was used in 5 cases. Two rows of plain catgut sutures, ½ to 1 inch above the other, were used to attach the urethrovesical junction, and the area of bladder just above, to the back of the pubic rami and symphysis. There

were usually 3 stitches in each row, 1 in the middle line and 1 on either side. Very little dissection and no suturing were carried out below the level of the internal meatus. By this simple technique the posterior urethrovesical angle was restored in 4 cases, albeit temporarily. The symptomatic results were not very satisfactory, however, and 2 women began to suffer a return of incontinence within a few weeks of operation (Figs. 8 and 10). In one of these the angle was then still present but there was funneling of the internal meatus and leakage of urine into the urethra (Fig. 10). This patient had previously had 3 anterior colporrhaphy operations and an Aldridge sling operation, all without effect on the incontinence. There was no sign of the sling at the time of the cystopexy. In the case of the second failure (Fig. 8) the angle was only temporarily restored by the operation, and when an Aldridge operation was carried out later with functional and anatomic success there was no difficulty in passing the fascial slips through the space of Retzius nor was there any evidence of adhesions in that area.

Fig. 7. Roentgenogram taken shortly after recurrence of incontinence 6 months after a Marchetti operation. Patient at ease. The posterior urethrovesical angle is obliterated.

THE EFFECT OF URETHROCYSTOPEXY ON OTHER URINARY SYMPTOMS

When cure of stress incontinence by any operative technique is accompanied by restoration of the urethra and bladder base to a good anatomic position, it will often be noticed that coexisting bladder symptoms such as diurnal frequency, urgency, and urgency incontinence also disappear. These symptoms are probably due to bladder irritability which is a reflex to mechanical stimulation of the nerve endings by the instability of the urethrovesical junction. The cure of such symptoms probably depends on some degree of fixation of this area achieved by the operation. This point is illustrated by the following case.

Shortly after the birth of her only child, at the age of 30 years, the patient had a Manchester operation performed for prolapse and stress incontinence. After a convalescence complicated by retention of urine and urinary infection the prolapse was cured but the urinary symptoms were more troublesome than before, and it was subsequently found that she had developed a urethrovaginal fistula, presumably as a result of the operation. Two attempts were made to close this fistula, but without success. She was first seen by one of us (T.N.A.J.) when she was 47 years of age and still suffering from a moderately large fistula in the middle third of the urethra. This was successfully closed by dissection and repair, accompanied by continuous bladder drainage by high vaginal cystostomy. The cure of the fistula, however, resulted in little improvement in the urinary symptoms, and 9 months after operation the patient still complained of a constant desire to micturate, extreme frequency which was mainly diurnal, urgency incontinence, as well as a slight degree of stress incontinence. Investigations including intravenous pyelography, cystometry, cystoscopy, and cystourethrography failed to show any local irritative lesion. The only abnormality detected was instability of the urethrovesical junction with descent and loss of the posterior angle on straining (Fig. 12a). In view of these findings it was decided with some trepidation to carry out a Williams type cystopexy. This resulted in slight elevation of the bladder base and urethra and restoration of the posterior urethrovesical angle (Fig. 12b and c). All urinary symptoms, which had been present for 17 years, were cured, and the

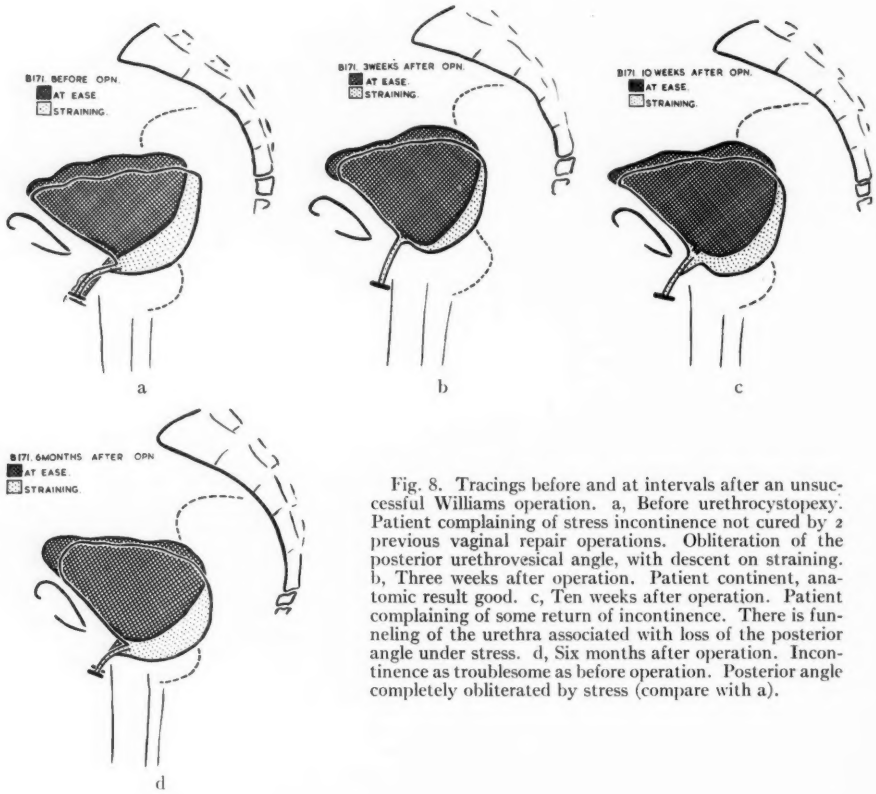

Fig. 8. Tracings before and at intervals after an unsuccessful Williams operation. a, Before urethrocystopexy. Patient complaining of stress incontinence not cured by 2 previous vaginal repair operations. Obliteration of the posterior urethrovesical angle, with descent on straining. b, Three weeks after operation. Patient continent, anatomic result good. c, Ten weeks after operation. Patient complaining of some return of incontinence. There is funneling of the urethra associated with loss of the posterior angle under stress. d, Six months after operation. Incontinence as troublesome as before operation. Posterior angle completely obliterated by stress (compare with a).

patient remained comfortable when last seen 6 months after the operation.

DISCUSSION

The roentgenologic findings in these cases confirm our previous conclusions about the importance of the posterior urethrovesical angle in the maintenance of urinary continence. All cases examined preoperatively showed roentgenologic evidence of loss of this angle when the woman was straining and sometimes even when she was at rest. Moreover, with the exception of 2 cases in the series, and a third case not included in the series because her last operation had been vesicourethrolysis, success or failure to cure stress incontinence could be related to restoration of the angle. Nevertheless, it should be emphasized that sometimes, as in these 3 cases, continence or lack of it does not depend on the angle. In these circumstances other anatomic changes play a part and need to be considered when a case is assessed or treatment is planned. In the original reports no claim was made that loss of angle is characteristic of *all* cases of stress incontinence (4, 5), and this tends to be overlooked by other workers and writers. It is a feature in at least 4 out of every 5 cases but not in all.

Further experience of cystourethrography leads us to add another note of practical importance. As the technique becomes standardized and its use more widespread, personal supervision of each case becomes impossible and this fact introduces sources of error. Unless carefully instructed and observed the patient may not strain sufficiently or at the right time, and films purporting to show the

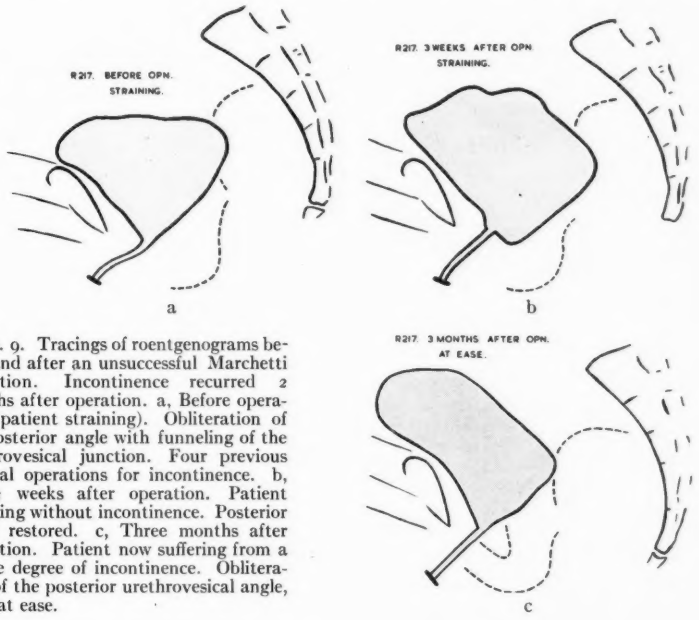

Fig. 9. Tracings of roentgenograms before and after an unsuccessful Marchetti operation. Incontinence recurred 2 months after operation. a, Before operation (patient straining). Obliteration of the posterior angle with funneling of the urethrovesical junction. Four previous vaginal operations for incontinence. b, Three weeks after operation. Patient straining without incontinence. Posterior angle restored. c, Three months after operation. Patient now suffering from a severe degree of incontinence. Obliteration of the posterior urethrovesical angle, even at ease.

bladder and urethra under stress can be deceptive. There was 1 case in the present series in which a woman suffering from stress incontinence after a Williams type operation appeared to have a normal angle under stress, but when the examination was repeated with one of us (H.R.) supervising the procedure it became clear that the woman had not been straining when the original film was exposed. A technique is being evolved by which the amount of straining exerted by the woman during roentgenography is measured by asking her to blow into a modified sphygomanometer. The pressure thus recorded should be not less than 40 centimeters of water (14 mm. of mercury). Errors may be made in the opposite direction too. Some women, when told to strain, misunderstand the instructions and they set in motion the mechanism of micturition; this always results in loss of angle, even in normal women.

Ever since the importance of the posterior urethrovesical angle was recognized it has seemed urgent to determine which muscles or other structures are normally responsible for its maintenance. For several reasons we have previously ventured the suggestion that it is more likely to be dependent on the intrinsic muscle of the bladder and of the urethrovesical junction than on extrinsic muscle either voluntary or involuntary. Cystourethropexy offers a means of helping to solve this problem because if the sites of sutures are varied it may indicate which tissue has to be stitched or tightened to restore the angle when it is lost.

In the Marshall-Marchetti-Krantz operation stitches are placed not only in the anterior and anterolateral aspects of the bladder and urethrovesical junction, but into the paravaginal tissues on either side of the upper urethra. In our experience this technique almost invariably corrected the angle although only temporarily in 2 cases. In the Williams technique, however, no stitches are placed below the level of the internal meatus yet the posterior urethrovesical angle was restored in 4 out of 5 cases, if only temporarily. This fact suggests once again that the angle is dependent on the intrinsic muscles of the urethrovesical junction rather than on any accessory muscles around the urethra and

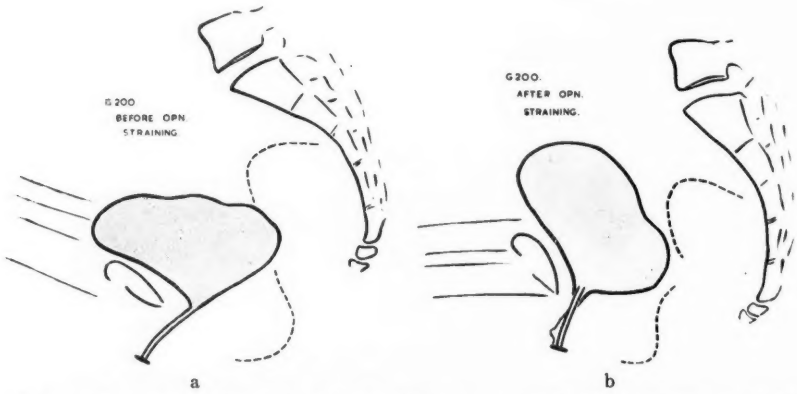

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Fig. 10. Tracings of roentgenograms before and after an unsuccessful Williams operation. a, Before urethrocystopexy, patient straining. Three previous unsuccessful vaginal repairs and an Aldridge sling operation. Posterior angle lost. b, Three weeks after operation. Posterior urethrovesical angle mostly restored even on straining, but there is funneling of the urethrovesical junction and leakage of fluid into the urethra. Incontinence recurred within a week of operation.

bladder. This conclusion is not yet a firm one, however, and another experience should be put on record.

A woman, not previously operated on, complained of frequency, urgency, and very occasional stress incontinence. Cystourethrography showed loss of the posterior angle. Other investigations gave negative results. At operation (T.N.A.J.) the space of Retzius was opened from above and a single mattress suture was placed across the front of the urethrovesical junction picking up the bladder muscle on either side. It was tied in the middle line, but neither the bladder nor urethra was attached to the pubic bones. It was hoped that this alone would correct the posterior urethrovesical angle. It had no demonstrable anatomic or symptomatic effect. This isolated observation again is not conclusive and further tests of this kind might well help to elucidate the problem. It is also relevant to point out that apart from one

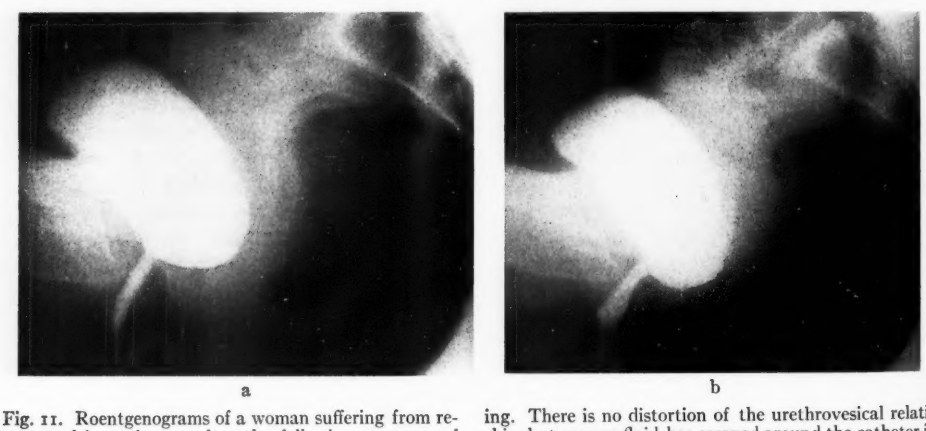

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Fig. 11. Roentgenograms of a woman suffering from recurrence of incontinence after the following sequence of operations: two vaginal repairs, fascial sling, Marchetti urethrocystopexy, and Mulvany vesicourethrolysis. a, At ease. Appearances are normal in all respects. b, Straining. There is no distortion of the urethrovesical relationship, but opaque fluid has escaped around the catheter into the middle urethra. In this instance the functional result bears no relation to the anatomy of the internal meatus as revealed by cystourethrography.

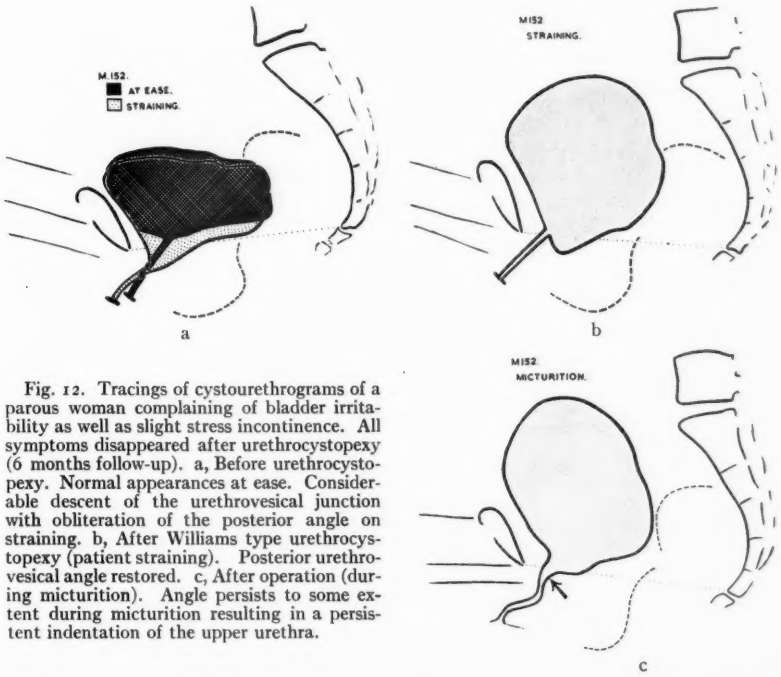

Fig. 12. Tracings of cystourethrograms of a parous woman complaining of bladder irritability as well as slight stress incontinence. All symptoms disappeared after urethrocystopexy (6 months follow-up). a, Before urethrocystopexy. Normal appearances at ease. Considerable descent of the urethrovesical junction with obliteration of the posterior angle on straining. b, After Williams type urethrocystopexy (patient straining). Posterior urethrovesical angle restored. c, After operation (during micturition). Angle persists to some extent during micturition resulting in a persistent indentation of the upper urethra.

sure this operation consisted of mobilization of the front of the bladder and the upper urethra and that this procedure, which is an essential feature of the Mulvany operation, did not correct the anatomic deformity usually associated with stress incontinence.

During the course of these studies some points of practical importance emerged. Cystourethrography after successful operations makes it clear how easy it is to overcorrect the original deformity or to create another deformity, and emphasizes the need in urethrocystopexy, as in sling operations, not to elevate or immobilize the urethrovesical junction too much. Our impression is that it is unwise to place stitches between the urethrovesical junction and the abdominal wall fascia —it causes too much uplift. Stitches between the upper part of the bladder and the abdominal fascia are unnecessary so there should be no fixation above the top of the symphysis pubis. Again, urethrocystopexy sometimes causes anterior funneling or loss of the anterior urethrovesical angle. This may be the result of placing sutures directly in front of the urethrovesical junction, and it is probably better always to place them only at the sides of the middle line no matter whether they be at the level of the urethra or at the level of the internal meatus and higher. Williams originally described placing the fixation sutures on either side rather than directly in the middle line; this would appear important to the correction of the posterior urethrovesical angle without causing other distortion.

SUMMARY

The effects of urethrocystopexy for stress incontinence in 24 women, as shown by cystourethrography, are described. Clinically, 19 of the women were "cured" within the limitations of a short period of follow-up.

The operation failed in 4 cases, almost immediately in 2, and in the others 2 and 6 months respectively after operation. Continued incontinence in the remaining case was due to a previously unrecognized urethrovaginal fistula.

Restoration of the posterior urethrovesical angle was the most constant feature of successful cases and *not*, as is often stated, elevation of the bladder base and urethra. Excessive elevation of the urethrovesical junction caused prolonged difficulty of micturition in 4 cases.

The Marshall-Marchetti-Krantz technique was used in 19 cases and there were 2 failures. All the cases of prolonged difficulty in micturition followed this method. The Williams technique was used in 5 cases and failed almost immediately in 2.

Modifications in technique for lateral cystourethrography are described and sources of error during roentgenography are mentioned.

It is noted that certain bladder symptoms, sometimes associated with stress incontinence and probably due to reflex bladder irritability from mechanical instability of the urethrovesical junction, can also be cured by urethrocystopexy or any operation which tends to fix an unduly mobile urethrovesical junction.

The mechanism normally responsible for maintenance of the normal urethrovesical relationship is discussed in the light of the findings.

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PULLED ELBOW

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Boston, Massachusetts

THIS condition is known by at least nine other scientific, colorful, and homely designations—partial dislocation of the radial head peculiar to children, dislocation of the head of the radius by elongation, partial epiphyseal separation of the radial head, painful paralysis in young children, Goyrand's injury, Malgaigne's luxation, housemaid's elbow, temper tantrum elbow, and elbow sprain. The commonest and most descriptive synonym, however, is simply pulled elbow, which is considered to be a subluxation of the head of the radius distally under the annular ligament. In spite of this array of designations, slight attention has been accorded this lesion in orthopedic literature of recent years. When encountered in orthopedic textbooks, it usually merits only casual discussion. Even in professional orthopedic discussions on elbow injuries it is rarely mentioned.

Boyette and London and Van Arsdale have reported that this lesion was first described accurately by Fournier, who wrote of it in 1671. Numerous and very excellent publications on this subject appeared widely on the continent in the latter part of the nineteenth century. The fact that pulled elbow was then considered an orthopedic problem is shown by Sidney H. Lindeman, who wrote in the *British Medical Journal* in 1885 that this lesion would ". . . frequently fall into the hands of the bone setters, and help to form the rock on which their reputation stands. For by rapidly and forcibly putting the joints through all their movements, they often blindly do the very thing required." Authors of more recent articles, however, are prone to refer to this loosely as a pediatric problem.

Today this injury is not generally understood, probably because it does not involve grave aspects. The diagnosis of this condition is all too frequently missed not only by the family physician, general surgeon, or pediatrician but also by the orthopedic surgeon. It would be difficult to think of a more simple diagnosis to make. We think that on many occasions this lesion is passed off as a sprain and treated accordingly, with a resultant period of pain, fretfulness, and unnecessary discomfort to a child until the pulled elbow is inadvertently spontaneously reduced by the patient himself. A careful history will usually result in the proper diagnosis. Almost without exception, a child's extended arm has been pulled or stretched when he is pulled up by one arm to a higher level, such as a curbing or streetcar step. Occasionally, a snap can be felt or heard by the parent when this occurs, and the child immediately cries out and thereafter maintains the arm limp, in a position of about 160 degrees of extension with the forearm in neutral or midpronation.

The subjective complaints are often misleading and frequently are referred to the wrist, midforearm, or even to the shoulder or clavicular region, and may be a source of needless roentgenograms and erroneous diagnoses. A careful examination in an anatomic sequence will reveal no evidence of fracture at any of these sites, but will reveal local tenderness at the radial head and a rubbery resistance to passive supination and extension beyond 160 degrees. These physical findings and history make the diagnosis of subluxation of the radial head distally under the annular ligament.

In children 5 years of age and under, the perimeter of the cartilaginous head is no larger and is generally smaller than the adjacent shaft; also it is an eccentric circle. Part of the edge of the radial head is rounded and part is rectangular, as described by Hutchinson in the *British Medical Journal* of January 2, 1886. Stone, in the *Journal of the American*

From the Orthopaedic Service, Boston City Hospital, Boston.

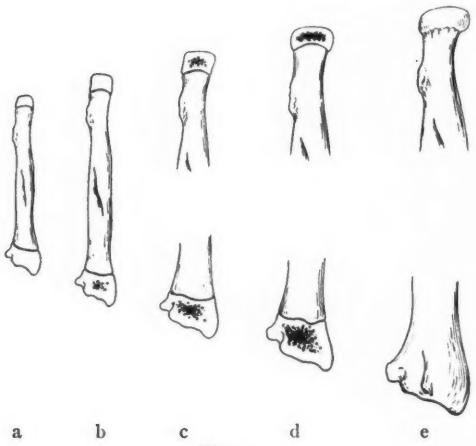

Fig. 1.

Fig. 2.

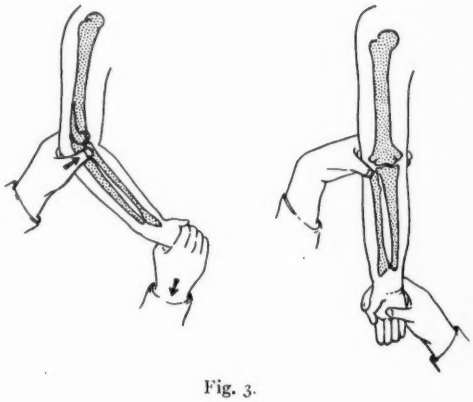

Fig. 3.

Fig. 1. Ossification of head of radius: a, birth; b, 2 years; c, 5 years; d, 8 years; e, 18 years. Note that the bony epiphysis of the radial head at 5 years of age has about the same diameter as the neck. At 8 years of age the radial head is larger in diameter than the neck of the radius. Redrawn from Piersol (3).

Fig. 2. Subluxation of annular ligament at head of radius. Anteroposterior view illustrates normal interarticular relations of annular ligament. Lateral view illustrates the subluxation of the radial head and the impingement of the annular ligament.

Fig. 3. Mechanism of reduction.

Medical Association of July 1, 1916, describes the abrupt rise from the neck to the head of the radius anteriorly, while laterally and posteriorly the rise is gradual (Fig. 1).

Only the annular ligament, which is intra-articular, is in close contact with the radial head and neck and maintains the proximal radius in position. When strong traction distally in the long axis of the radius occurs, the radial head is displaced under the annular ligament. The eccentric contour of the radial head slips under the annular ligament and becomes locked. When traction is released, the annular ligament assumes a more proximal position on the radial head and may become impinged between the radial head and capitellum (Fig. 2). Such sudden displacement of the radial head under the annular ligament accounts for the frequently noted audible or palpable click. This theory of the mechanism of production of pulled elbow is described in Piersol's *Human Anatomy*.

In the vast majority of cases, when examination reveals no deformity or evidence of fracture and no abnormal x-ray findings are noted, one may proceed to correct this anatomic lesion by manipulation. No anesthesia is required. The involved elbow is gently grasped in such a manner that the thumb is placed just behind the radial head. With the other hand, the patient's wrist is grasped and the forearm is slowly supinated and extended (Fig. 3). The rubbery resistance which is noted as this is done suddenly ceases and, at that moment, a definite click is heard and felt. If this does not occur, the opposite procedure as described by numerous writers on this subject may be tried—flexion of the elbow with simultaneous pronation of the forearm. Occasionally flexion

of the elbow and forearm supination are required to obtain a reduction. Some writers described flexion with pronation, or flexion with supination as the proper manipulative procedure for this condition.

Almost immediately, the child is symptom-free, happy, and co-operative. In cases in which the diagnosis is missed and the injury considered a sprain, as frequently happens, the forearm is placed in a sling with the radial head still in subluxation. The child then goes on his way in distress until such time as extension and supination are, inadvertently, carried out. The displaced radial head thus becomes replaced. If this anatomic lesion has been present for several hours, some edema of the annular ligament and capsule may be present and it may require several days for all symptoms to subside.

In all of our cases, a sling is applied with a request that it be worn for 5 to 7 days. Occasionally a plaster of paris splint is applied, but it is not thought that this is necessary. Prereduction and postreduction roentgenograms were taken in the majority of cases in this series and no abnormal findings were ever noted. On the fracture service of the Boston City Hospital the diagnosis has often been missed because of the mild symptoms and frequent accidental reduction of the subluxated radial head during the examination of the patient. After a period of particular attention to this condition, however, it has actually been found to occur quite commonly. Van Arsdale reported an incidence of pulled elbow of 1 per cent in purely surgical cases of all ages, and about ½ per cent for children, including all ailments, under 10 years of age. Our study indicates the much higher incidence of 3 per cent, the condition occurred with greater frequency on the left side, and 62 per cent of the cases were in females. Two private cases (A.P.A.) with long follow-up periods, not included in this series, are mentioned here. One case was followed for a 3 year period and 1, with a 10 year follow-up, had 3 recurrences of pulled elbow on the same side. Both are now normal and have normal roentgenograms.

SUMMARY

1. Subluxation of the radial head distally under the annular ligament at the proximal radioulnar joint, commonly called pulled elbow, has long been considered one of the more common injuries to the upper extremity in young children, and it is considered a distinct anatomic elbow injury. This diagnosis can be and often is overlooked, even if the examiner knows the real nature of the lesion.

2. An almost uniformly consistent history of sudden, forceful traction in the long axis of the radius causing the subluxation of the radial head under the annular ligament is obtained.

3. The subjective complaints vary widely. Numerous patterns of referred pain in the upper extremity are noted. Fretfulness and patient's refusal to use the limp arm are nearly always noted. A careful and logical examination of the upper extremity reveals little other than elbow tenderness to palpation, particularly at the radial head, and a rubbery type of resistance to attempted passive extension and supination.

4. We find the incidence of pulled elbow considerably higher than reported by Van Arsdale—27.5 per cent of cases of fractures or dislocations of the elbow in children under 10 years of age. Pulled elbow was diagnosed in 3 per cent of all children 8 years of age and under who were seen in the plaster room, regardless of the type of trauma or lesions present. The average age of 2.6 years coincides with the average age when pulled elbow is incurred, as reported by Anderson and Poinsot. Pulled elbow is seen in greatest frequency on the left side. There were no cases of pulled elbow in children over 8 years of age. These statistics were derived from an analysis of the 3,390 children, 10 years of age and under, who were seen in the plaster room of the Boston City Hospital over a 2 year period.

5. Immediate reduction without anesthesia by passive extension and supination with light pressure applied to the patient's radial head has been quite uniformly successful in our hands. No postreduction immobilization other than a sling for a few days is required. We think that the incidence of recurrence is probably quite high.

CONCLUSION

Subluxation of the radial head at the proximal radioulnar joint is a definite and distinct anatomic lesion of the elbow in young children under 8 years of age. This lesion is relatively common and deserves a more prominent place in our armamentarium of diagnoses, discussions, and treatises, as well as in orthopedic and traumatic surgery texts.

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EDITORIALS

SURGERY
Gynecology and Obstetrics

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JUNE, 1954

THE RIGHTS OF THE PATIENT

IT HAS often been said that the doctor who treats himself has a fool for a patient. Likewise, many physicians think that they should not prescribe for or operate upon members of their immediate family. Perhaps the vast majority of surgeons are willing to subscribe to this concept. On the other hand, where can a patient find a surgeon who is more anxious for him to have the very best surgery, in the safest manner, with the least discomfort and inconvenience than a member of his own family?

My surgical residents have repeatedly been told that there is only one inflexible rule on my service, namely, that every patient, either ward or private, regardless of race, color, or creed, be treated as if he were a member of his family or indeed as he himself would want to be treated under such circumstances. It seems to me that the surgeon's aim should not be to achieve such emotional detachment from his patient that he can practice pure "scientific medicine" upon him as the 130th case in such and such a series, but rather to look upon him with such kindliness that he treats him as if he were one of his family.

The teaching of such a close relationship of the surgeon to his patient must start with the junior surgical intern and even so the attitude of the chief in this regard will cast its shadow. A simple example: The surgical intern is called in the middle of the night because a patient who had a gastrectomy the previous morning has been unable to void. The simplest thing to do and the quickest way for the intern to get back to bed is to catheterize the patient immediately. But you and I know that if that patient were a member of his family he would make every effort to get him to void normally. He would not stand him up barefooted on a cold floor in a cold ward with a hospital gown reaching slightly below his umbilicus and expect him to void. He would get him a warm bathrobe, some warm socks and slippers, take him to a warm bathroom, and let him sit on the toilet and try to void in the most relaxed manner possible.

Likewise, if upon his night rounds, the junior surgical resident finds a patient who has had a pneumonectomy that day with a lot of secretions in his remaining lung, the easiest thing to do is to tell the nurse to keep after the patient to cough out the secretions during the night. But you and I know he would not be willing to take the risk of atelectasis of the remaining lung with a member of his own family. He would come down and see him every 2 or 3 hours during the night and aspirate his trachea if the patient could not clear his chest completely by coughing.

One may ask, how can a surgeon run a teaching service if every patient is to be given the

very best treatment? Would not the chief of the service have to operate upon every patient if he were to give him the very best treatment? Some years ago there was a saying in some surgical circles that "every young surgeon has to fill his grave yard." We believe that such a statement no longer holds and it is our objective for every patient on our wards, as well as in the private section, to get the very best surgical care. I believe that a chief should never leave a resident with an operation until he thinks that that resident can do the operation as well as he can. He would not if the patient were a member of his family. This does not mean that the resident could necessarily do the operation as rapidly as the chief but that the resident knows the essential steps of the procedure and the end result of the operation would be the same. Unless the resident has seen the procedure often enough and has been "nursed through" it often enough to feel at home with it, he should not be left alone.

The primary objective of any teaching hospital is to give its patients the very best care, regardless of their economic status. Only by so doing can we give our young surgeons the desire to do likewise. The young surgeon should receive adequate training before being left on his own, and, above all, should be trained to call for help when he needs it.

When a patient dies on a teaching service when he might have been saved had he been operated upon by a staff man, that teaching service has failed in its mission, for there is nothing so important to teach the surgical resident as saving the patient's life. With modern anesthesia, there are few conditions in which speed is important in the operation. The surgical resident can be "nursed through" most procedures without jeopardizing the patient's life. When time is important because of the patient's condition, the operation should be performed by a staff man or the chief. The thought that the surgery on the ward patients belongs to the residents is not tenable under such circumstances. To teach the young surgeon to give the patient anything less than the best that can be obtained for him is to fail miserably in our teaching.

It may be asked, how is it possible to advance the fields of medical knowledge if the surgeon is to treat every patient as a member of his family? How can he try out new operations? We believe that the laboratory is the place to try out new procedures insofar as it is possible to do so. The surgeon should have tried out his problem in the laboratory and thought through it sufficiently to believe in it himself. He should not try it on his patient unless he would want to have it done on himself under similar circumstances. If the procedure does not seem sufficiently reasonable to him so that he would want it done on a member of his family, he should not do it on his patient. It must be admitted that at times it may be easier to subscribe to this concept than to make every decision by its standard. This is true because the surgeon is often in the position of not knowing what he would want done for himself or one of his family under such circumstances. Obviously, when the circumstances are desperate, the surgeon would be willing for a member of his family to be submitted to a greater than normal risk. It is perhaps as great an error to deny a dying man a chance to live because of the fear of an operative mortality as to operate upon a good risk patient needlessly.

We who are surgeons inevitably will make errors in judgment in the course of our surgical practice. However, we will make fewer such errors if we can train ourselves and our residents constantly to keep before us the "family" yardstick in providing our patients with surgical care. JULIAN JOHNSON.

RUPTURED AORTIC ANEURYSM—A SURGICAL EMERGENCY

SYMPTOMS from an abdominal aortic aneurysm mean that it is expanding, pressing upon adjacent structures, or rupturing. Perforations in the wall permit greater or lesser quantities of blood, or hemoglobin by-products, to escape retroperitoneally; and if this dissection occurs posteriorly the pain is in the back, if anterior the symptoms and signs are those of peritoneal irritation. These symptoms are associated with a pulsating mass, and roentgenograms will reveal the calcified wall of the aneurysm.

The diagnosis of an abdominal aortic aneurysm usually has been made before rupture occurs, but it is not uncommon for symptoms caused by rupture to call attention to the aneurysm for the first time. It is likewise not unusual for an operation to be performed on a painful or tender abdominal tumor which only then is discovered to be, in fact, an aneurysm.

Clinical studies by Estes and others showed that the life expectancy of those who have the lesion is appreciably shortened, but even of more significance is the fact that if symptoms appear a fatal issue from rupture is apt to occur within a year. Most important, however, is the observation that fatal rupture frequently is preceded by repeated episodes of pain or mild shock extending over a period of days or weeks before a final hemorrhage settles the issue. This delay no doubt occurs because of the large thrombi so frequently found in these aneurysms, which temporarily occlude the site of rupture. Therefore, one often has time to prepare for surgical intervention, or to transport the patient to a hospital where it can be done.

Although it may be necessary to employ such means as wiring of the aneurysm, the experience of Dubost, DeBakey and Cooley, Bahnson, and others, including our own, has clearly demonstrated that resection of the diseased abdominal aorta, with replacement by homograft is not only anatomically feasible in most instances, but is attended by a low operative mortality rate. It is also clear that one can operate after rupture has occurred, obtain control of the situation, and replace the aneurysm with an aortic homograft. In fact, we have been able to perform the operation successfully even after massive hemorrhage has resulted from a large rupture.

It is therefore important to consider a patient with signs or symptoms of rupture of an abdominal aortic aneurysm as having a surgical emergency; operation should be performed as soon as the proper arrangements can be made, and every effort directed toward resection of the aneurysm with restoration of continuity by aortic homograft.

FRANK GERBODE.

THE SURGEON AT WORK

NEW METHOD OF PELVIC TRACTION FOR THE RELIEF OF LOW BACK PAIN

SAMUEL VARCO, M.D., Buffalo, New York

TREATMENT of the low back syndrome, due to injury or disease, under present methods leaves much to be desired. A method for the application of pelvic traction in treatment of low back pain is presented. It is believed that the method is simpler, more efficient, and more certain of results than those in present use.

Application of traction is accomplished by the use of a special pelvic belt with strips of webbing coming down each side to a spreader. The desired weight is exerted through the middle of the spreader. The pelvic belt should have a soft, pliable portion that will cup over the crest of the ilium, and have properly placed slip buckles. The belt is individually fitted to each patient. In addition, 4 strips of 1 inch, nonelastic webbing, 2 of them 5 feet long and 2 of them 3 feet long, are required, as is also a single wooden spreader foot bar with slots at each end to receive the webbing and a hole in the center to insert the sash cord weights.

From the Department of Orthopedic Surgery, Buffalo Hospital of the Sisters of Charity, Buffalo, New York.

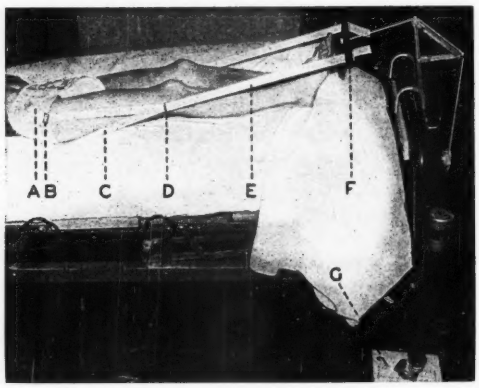

Fig. 1. Special pelvic traction belt consisting of: *A*, soft, pliable hood over the iliac crests, *B*, slide buckle, *C* and *E*, nonelastic webbing, *D*, Dee buckle, *F*, common spreader bar—18 to 20 pounds through center, and *G*, 10 inch elevation at foot of bed.

The belt is placed around the waist and pelvis of the patient, the 5 foot strips of webbing are inserted through the slip buckles of each side, from anterior to posterior ("swing type"), and through the Dee rings of the 3 foot strip so that the apex will be at the level of the knee. The 3 foot strips of webbing are then carried to the single spreader, the entire strip adjustment now being in the shape of a Y (Fig. 1). Both sides are adjusted to equal length, and the desired amount of weight is applied through the middle of the spreader. The cord pulley and its weights are suspended over the foot of the bed in the usual manner.

The device is easy to apply and is well tolerated by the patient; it accomplishes everything that is hoped for in leg traction and brings about maximal results in a much higher percentage of cases. Leg traction is trying, not only to the patient but also to the nursing and house staff, and often the patient eventually removes the leg adhesive regardless of the doctor's orders. With pelvic traction, on the other hand, the patient is comfortable and co-operative, since there is free movement of the lower extremities and this also makes for easier nursing care (Fig. 2). The method has other advantages. None of the complications that often develop with the use of leg traction have been noted. It causes no swelling of the knee or ankles, no reactions such as redness, swelling, or rash so often caused by adhesive plaster, and it eliminates one possible cause of phlebitis of the legs.

Pelvic traction is felt by the patient, not in the knee or hip joint, but at the sacroiliac articulation and along the spine. In instances in which too much weight was applied, the traction has even been felt as high as the dorsal cervical region. The amount of traction actually obtained when adhesive plaster is applied to the skin of the leg for low back pain is questionable. Certainly, it is indirect in type. In pelvic traction, with the

pull being exerted on the crest of the ilium, the traction is direct because of the intimate relationship of the sacroiliac joints, the lower spinal vertebrae, the musculature, and the ligamentous tissues to the pelvic bones.

The method has been used in over 200 cases of various types of low back injury, including cases of slipped disks, fractures of the pelvis, and fractures of the lumbar vertebrae. Most of the patients were treated at the Buffalo Hospital of the Sisters of Charity; several were treated at home; the remainder were treated in other hospitals in the Buffalo area. Approximately 90 per cent of them have claimed improvement. Freedom from pain within a matter of hours was recorded in many instances, and in a very high percentage of severe cases, the patients were able to return to work in from 3 to 4 weeks.

All that is claimed for the method is that it does everything expected of leg traction but does it more efficiently and with more certain results. It is applicable to any case in which relaxation and decompression of tissues is hoped for; that is, in injuries involving the lower half of the back, some fractures of the pelvis, and some fractures of lumbar vertebrae.

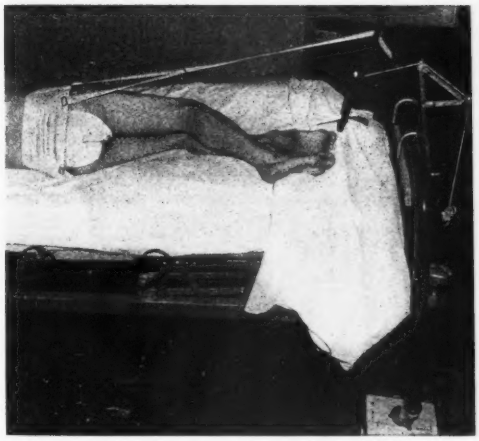

Fig. 2. The maneuverability of the patient that is possible with this apparatus enables simultaneous employment of other modalities.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

PART 2 of the *Textbook of Gynecology*[1] is based upon a former book by Brewer entitled *Gynecology*, published by Thomas Nelson and Company in 1950.

The original groundwork for this textbook was accomplished in the preparation of lectures for the students of Northwestern University Medical School. The author has selected as chapter headings a symptom such as leucorrhea or abnormal bleeding and then considers the various entities which may produce the symptom. This method of teaching has numerous advantages and a text so arranged is of great benefit to the undergraduate student. When confronted by a symptom he has elicited in the clinical history, he is enabled to eliminate in orderly fashion the conditions not pertinent. In this way he is taught to organize his thinking in the same way that he must organize his thinking in the daily practice of medicine.

In Part 1 the author employs the other method of teaching, namely, the elaboration of individual entities such as fibroids, carcinoma of the cervix, and endometrial carcinoma. This addition to the original text was in response to many requests that the author express his opinions on these important clinical entities. This addition has increased the value of the book for students but will not satisfy the graduate student searching for authentic evidence in support of the etiology, diagnosis, and management of gynecologic disease. It is hoped, therefore, that Brewer will continue to review and edit this text for undergraduate teaching and prepare a separate text for the graduate student and the reference library, for his views as expressed in the chapters on carcinoma of the cervix, fibroids, and endometrial carcinoma indicate a rich clinical experience and pleasing style which should be made available to the medical profession at large.

HERBERT E. SCHMITZ.

THE 591 page monograph *A Practice of Thoracic Surgery*[2] by d'Abreu who is a thoracic surgeon, Queen Elizabeth Hospital and the Children's Hospital of the United Birmingham Hospitals, England, is divided into seven parts as follows: (1) Anatomical and Physiological Considerations; (2) The Surgery of Pyogenic Infections; (3) Pulmonary Tuberculosis; (4) Neoplasms of the Lung and Trachea; (5) Surgery of the Mediastinum including chapters on Surgery of the Heart, Great Vessels, and Pericardium, Congenital Heart Disease, and the Esophagus; (6) Some Miscellaneous Conditions—Surgical Aspects of Pulmonary Emphysema, Pulmonary Hydatid Disease, and Thoracic Injuries; and (7) Thoracoabdominal Surgery.

In the preface the author states that "In choosing the title of this book I deliberately chose the words 'A Practice' rather than 'The Practice of Thoracic Surgery.'" He has made no attempt at a comprehensive account of the various aspects of thoracic surgery but rather has given a limited and often a personal account attempting, in his own words, "to clear my views as to my own practice." The author states that it is not intended "for my own colleagues in the thoracic field," yet in many sections his presentation falls short of that degree of comprehensiveness which will enable a serious student to gain the proper perspective.

The description of the surgical anatomy of the lungs is well done and will be valuable to the man learning the technique of pulmonary resection.

The chapter on pulmonary function written by K. W. Donald is a sound presentation of current methods and their limitations.

In this book one encounters many ideas which are contrary to current concepts and practice in this country. By way of illustration here are a few: that a patient should be hospitalized for a week before a major thoracic operation; that "in chronic lung or pleural infection oedema of the posterior lower chest and the lumbar area is common"; that "under good tuition the co-operative patient soon learns to control his breathing so that, at will, he can ventilate a lung or a single lobe more freely than their counterparts sited elsewhere;" that "seventy-five percent of lung cancers are in areas of the bronchial tree visible at bronchoscopy and are suitable for biopsy"; that it is increasingly difficult to accept the thesis that bronchial adenomas are malignant tumors.

The task of writing a text in the field of thoracic surgery where spectacular developments have occurred so rapidly is admittedly a difficult one. Any presentation which attempts to be comprehensive is obsolete by the time that it reaches print. On the other hand, any effort which lacks comprehensiveness must necessarily have many serious shortcomings.

[1] TEXTBOOK OF GYNECOLOGY. By John I. Brewer, B.S., M.D., Ph.D. 532 pages, 146 illustrations. $10.00. Baltimore: The Williams & Wilkins Co., 1953.

[2] A PRACTICE OF THORACIC SURGERY. By A. L. d'Abreu, O.B.E., Ch.M., F.R.C.S. 591 pages, illustrated. London: Edward Arnold & Co.; Baltimore: The Williams & Wilkins Co., 1953.

The most valuable portions of the book are those that deal with the descriptions of operative technical details. These accounts will be of considerable interest and will make profitable reading for the surgeon learning operative procedures in the chest. There are many excellent reproductions of roentgenograms and a large number of helpful line drawings. W. D. SEYBOLD.

SINCE the first edition, published in 1934, Brailsford's textbook on *The Radiology of Bones and Joints*[1] has held an eminent place in the reference library of roentgenologists and orthopedic surgeons. The completely revised fifth edition maintains its position as one of the foremost encyclopedias on orthopedic radiology, recording the vast and long experience of a roentgenologist with an intense interest in compiling and analyzing an amazing amount of material. The book contains 828 pages with over 725 illustrations plus an index and an extensive bibliography.

The reviewer questions the advantage of the chapter arrangement into body regions—the hand, wrist, elbow, and knee—with repetitious discussion of scurvy, rickets, syphilis, and tuberculosis, in each chapter. It would seem preferable to discuss each disease entity as a whole, with all its bone and joint manifestations.

It is hoped that in any future edition, the author will replace all indistinct and, therefore, useless illustrations: for example, the radiographs depicting osteomyelitis on page 204 and many others, and that he will find it possible to have larger illustrations since the very small ones are entirely unsuitable for the beginner and even difficult for the advanced student. The line drawings of the pathology of rickets and scurvy on page 109 are likewise unsuitable for the beginner and could be replaced with appropriate roentgenograms to advantage. Most of the illustrations are devoid of right or left markers, and in some instances it would take a trained radiologist to detect which side has the lesion when both sides are shown. No effort has been made to have the descriptive text and corresponding illustration on the same page; for example, on page 152 it refers the reader to Figure 218 without giving its page (Fig. 218 is located on page 210 after many seconds of searching). This happens with annoying frequency.

Some of the illustrations are poorly chosen. For example, Figure 189, page 182, purports to show a tibia varus when actually a tibia valgus is shown; Figure 279, page 269, is captioned "coxa valga" of the hip, whereas the illustration shows a femur externally rotated in lateral projection in which position all femurs show "coxa valga."

Dr. Brailsford's insistence that osteoid osteoma is nothing more than a chronic bone abscess, because it looks like one on the roentgenogram, and because 1 or 2 cases he cites cleared up with chemotherapy (with no biopsy confirmation), is contrary to the best existing evidence; and one cannot help but wonder why he ignores the contributions of the pathologist.

Similarly, it is regrettable that an authority as widely read as Dr. Brailsford should impugn the accuracy of biopsy examination in suspected bone tumor cases and maintain a position that x-ray diagnosis is the superior method. He could have stressed the importance of the need for the closest co-operation between the radiologist and the microscopic pathologist as is practiced in the leading bone tumor centers. Very few radiologists can accumulate, in their professional lifetime, sufficient experience in bone tumors to maintain Brailsford's viewpoint, and even those with wide experience are not inclined to dispense with the pathologist's help. The author's long list of the dangers inherent in biopsy do not seem tenable in the light of everyday experience.

Brailsford's book is recommended as a "must" on the shelf of every practicing roentgenologist and orthopedic surgeon. It is recommended for the beginner with reservations, because of the rather small, and in some instances, poor illustrations and the one sided presentation of controversial subjects.

It is hoped that there will be future editions of this very useful book. CHARLES W. BREIMER.

THE monograph, *The Breast in Roentgen Diagnosis*,[2] consisting of 194 pages, has 307 illustrations. There are about 150 superb full page illustrations, and more than 20 pages half occupied by illustrations, all with good explanatory legends. Obviously textual material must be very sparse. Essentially the book is an atlas which illustrates the technical aspects of the roentgenologic examination of the female breast, and depicts the roentgenographic manifestations of anatomicopathologic changes produced in the substance of the breast by almost every known variety of disease that affects the mammary gland, but chiefly neoplastic disease, and especially malignant neoplastic disease.

The expressed purpose of the book is to provide a wider familiarity with the diagnostic possibilities of roentgenography of the mammary gland, and to promote wider application of this diagnostic procedure. It should, the author contends, become a part of the routine clinical investigation of the female breast. He holds that the discredit nowadays attending this particular application of roentgenography is no longer justifiable. He hopes to convince the sceptical that with the modern x-ray tube and the modern x-ray film, roentgenography has a very real and very valuable contribution to make to the diagnosis of disorders of the mammary gland, obviating in a significant number of instances the need for biopsy, and affording data which enable the

[1] THE RADIOLOGY OF BONES AND JOINTS; AN INTRODUCTION TO THE STUDY OF TUMOURS AND OTHER DISEASES OF BONE. By James F. Brailsford, M.D., Ph.D., F.R.C.P., F.I.C.S.(Hon.). 5th ed. $19.00. 875 pages, 725 illustrations. Baltimore: The Williams & Wilkins Co., 1953.

[2] THE BREAST IN ROENTGEN DIAGNOSIS. By Raul A. Leborgne, M.D. English translation by Lucy Crocker De Leborgne. 194 pages, 307 illustrations. Montevideo: Impresora Uruguaya S. A., 1953.

surgeon to plan his therapeutic procedure more advantageously to the patient.

In general, it is a convincing presentation. The lesions are not difficult to see on the roentgenograms reproduced in the book. Photographs of the lesions represented on the roentgenograms are exhibited, usually with photomicrographs, to prove their histologic identity. It does not look difficult in any way. Two projections of the breast in opposing directions of the x-ray beam and there you have it: a picture which is represented not only to distinguish normal from abnormal, but also neoplastic from nonneoplastic, and malignant neoplasms from benign ones.

It is difficult to believe that it actually is as simple as that. If roentgenography of the breast has not been accepted widely, it is not because competent investigators have failed to give it a good try. Mammography or mastography, as this roentgenographic procedure has come to be known, is no novelty. It enjoyed quite a vogue in the decade following Warren's original presentation of the subject in 1930. This investigator and others, notably Lockwood, J. Gershon-Cohen, and Seabold, produced diagnostic roentgenograms and had demonstrated a high diagnostic accuracy for the procedure before 1940. The pitfalls and inherent technical difficulties of the approach were also recognized. General enthusiastic acceptance, however, was not realized. Many who tried to apply the procedure, although perhaps not diligently and intensely enough, came to consider it somewhat in the light of glorified transillumination. Interest lagged. Leborgne became interested in the early years of the last decade. Using the small focal spot of the modern x-ray tube, more modern film with finer grain, and very careful control of exposure factors, he showed that roentgenograms of diagnostic quality superior to those made before could be produced. The interest of others, notably that of J. Gershon-Cohen in this country, was reawakened by Leborgne's early publications. It appears now that today the roentgenographic technique is better, and the diagnostic criteria are correspondingly superior and better defined than they were 10 or 15 years ago.

One is prompted to raise the question, "Is the yield worth the effort?" The technique of procuring diagnostic roentgenograms of the female breast is a tricky one. Proper exposure factors continue to be difficult to estimate. The breasts—both must be subjected to examination in all instances—must be manipulated considerably, so that for obvious reasons, not just any technician can be put on the job. While the actual roentgenography is probably the most vexing problem, the interpretation is also attended with considerable difficulty. A large experience with the normal breast under all conditions of age, function, adiposity, and with all types of organic abnormality will have to be acquired by anyone who expects to deliver a diagnostic opinion that deserves respect, especially from those who have acquired the status of experts in the clinical diagnosis of disorders of the mammary gland. The opinion of a Leborgne or of a J. Gershon-Cohen will be valuable indeed. But the person with only an occasional experience, or one who has just read the books without having acquired an intimate personal knowledge of the pathology of the breast, well correlated with personal experience with the roentgenographic representations of these pathologic changes, can hardly expect to have much confidence in his opinion himself, much less hope to enjoy the confidence of those who consult with him. This, of course, is true of any roentgenologic diagnostic procedure, but it seems to this reviewer, that here is a very specialized field in which adequate diagnostic experience will hardly be achieved short of a prolonged day by day application of the method to a large number of patients. Is the yield, the contribution of the method, worth this expenditure of time and effort? Perhaps it is, and time may tell. Certainly the answer cannot be given without placing mammography in direct competition with the standard clinical investigation now in use and advocated by those experts whose knowledge and experience give them a genuine right to that appellation.

HARRY M. WEBER.

"LET us make surgery safe for the patient," would appear to be a concise review of Luigi Imperati's book *Trattamento del malato chirurgico*."[1] This well written volume succeeds in correlating the pathologic physiology of the surgical patient with the clinical picture.

Beginning with the psychologic aspect of surgery, in so far as it affects the patient, the author discusses the stress reaction, as outlined in Selye's hypothesis, and depicts the operation as a phenomenon of controlled trauma. The author maintains the focal point of interest on the pathologic physiology of the patient, pushing technique to the background to the advantage of the medical man's viewpoint.

The management of the patient from the preventive aspect overshadows the actual problem of the control of complications, although the latter problem is thoroughly discussed in a separate section. Throughout the entire 684 pages, the author has taken advantage of the work of others. The extensive bibliography contains men prominent in their respective fields throughout the world.

The book is divided into four sections: (1) generalities of pathologic physiology; (2) preparation and control of the surgical patient; (3) postoperative complications and their treatment; (4) management and treatment of the patient in respect to the specific site of operation.

In the last section individual pitfalls as regards the specific area to be operated upon are discussed. Thoracic surgery is in this manner separated from abdominal and gynecologic surgery.

[1] TRATTAMENTO DEL MALATO CHIRURGICO; FISIOPATHOLOGIA E CLINICA DELL'OPERATO. By Prof. Luigi Imperati. Preface by Prof. Luigi Torraca. 684 pages, 116 illustrations. L. 7.000. Napoli: Casa Editrice V. Idelson di E. Gnocchi & F., 1953.

There is a wealth of up-to-date information in this book that makes it a valuable addition to the medical as well as surgical library.

FRANK W. PIRRUCCELLO.

THE 600 page volume of *Clinical Endocrinology*,[1] including 75 pages of bibliography, has been written for the general physician and those "who wish to become endocrinologists." Primarily clinical in scope, this book is the result of the author's observation in the wards of St. Bartholomew's Hospital in London. The clinical problems of endocrine disease and the diagnostic procedures have been given in detail. Physiology is only briefly outlined and the anatomy entirely deleted.

The volume is sparsely illustrated with 59 black and white illustrations and 2 color plates. Most of the text deals with the best understood endocrine glands such as thyroid, adrenals, and the female endocrine system. This part of the work is particularly well done, although not necessarily up to date. The parathyroid and pituitary glands and male genital system are not as completely described.

The use of ACTH and cortisone is outlined and somewhat outdated. The treatment of obesity by use of the English diet will not be appreciated by the American physician. Arithmetical errors appear in the chapter on obesity as the author converts kilograms to pounds.

One's chief criticism has to do with the method of the presentation of the subject matter. Each chapter is written as though it were a review of the contemporary literature of the subject. As a result there is constant quotation from the source material along with frequent references to the bibliography. This becomes somewhat of an annoyance to the reader. In general, however, this volume comprises a good outline of our present knowledge of the endocrine field and its development up to 1950.

HOWARD A. LINDBERG.

IN the opening sentence of the introduction to the large volume *The Physiopathology of Cancer*[2] the editors state that their purpose is "to bring together in one volume the present-day knowledge in all the active fields of cancer research." To do this they have asked 28 distinguished students of the problems of neoplasia to contribute chapters describing the state of knowledge in their own particular field.

In Part 1, biology, there are discussions of the pathology, genetics, and natural history of the transplantable tumors and of tumors induced by chemical, viral, and hormonal agents. These chapters, which have been written by H. L. Stewart, I. N. Dubin, T. B. Dunn, H. I. Firminger, G. W. Woolley, W. U. Gardner, C. A. Pfeiffer, J. J. Trentin, J. T. Wolstenholme, F. Duran-Reynals, G. D. Snell, and A. Tannenbaum, are excellent giving not only adequate presentations of the subjects but also extensive bibliographies. The chapters on the chemically induced tumors are especially fine and fill a real need, for no similar review of these tumors exists. Most aspects of current research into the biologic properties of experimental tumors in animals are adequately treated in this section of the book, although there is an occasional baffling omission. For example, I have been unable to find any mention of the important recent work on the mechanism of metastasis.

Part 2, chemistry and physics, contains 8 chapters dealing with the mechanism of carcinogenesis (A. Haddow), chemical alterations of neoplasia (R. J. Winzler, G. Schmidt, and W. H. Fishman), cytochemistry and histochemistry (G. Gomori), experimental chemotherapy (D. A. Karnofsky), and the experimental aspects of radiation (L. D. Marinelli and A. M. Brues). Of these the chapter on cytochemistry is tantalizingly brief and one wonders why the author did not see fit to discuss more fully the interesting contributions which are being made in this fertile field. For example, some discussion of the findings in regenerating liver and other tissues would seem appropriate. Haddow's chapters on the mechanism of carcinogenesis are most stimulating and thought provoking as usual, but I wonder at the reason for not including discussions of cocarcinogens and anticarcinogens.

Part 3, clinical investigation, contains chapters on steroid metabolism (L. E. Engle), clinical investigations (F. Homburger), environmental factors (W. C. Hueper), and statistical studies (H. L. Lombard), and Part 4 chapters on diagnostic tests (F. Homburger), chemotherapy (A. Gelhorn), exfoliative cytology (S. C. Kasdon), radiation therapy (L. H. Garland), and the use of isotopes in diagnosis (B. Selverstone). Altogether these chapters occupy about 300 pages in contrast to the nearly 700 pages devoted to the chapters dealing with laboratory experimentation. This is probably a reflection of the fact that in recent years clinical investigation has lagged far behind laboratory studies of neoplastic diseases. Not only is this disparity evident in the number of publications, but also in their quality as these chapters make abundantly clear. Unrealized opportunities exist for useful investigation of the nature of neoplasia in humans and the time now seems ripe to pursue such studies. Many ideas for such studies can be obtained from these chapters for they give a good survey of work already done and make clear the nature of the problems that still exist. In my opinion the value of this part of the book would be increased by including sections on the natural history of untreated human tumors, and on the results of twin studies into the genetic factors involved in human cancer. I was also surprised at

[1] CLINICAL ENDOCRINOLOGY. By Allan William Spence, M.A., M.D.(Cantab.), F.R.C.P.(Lond.). 696 pages, 59 illustrations. $12.50. New York: Paul B. Hoeber, Inc., 1953.

[2] THE PHYSIOPATHOLOGY OF CANCER; A TREATISE FOR INVESTIGATORS, PHYSICIANS AND STUDENTS. Edited by Freddy Homburger, M.D., and William H. Fishman, Ph.D. With 28 contributors, foreword by C. C. Little. 1031 pages, 150 illustrations. $18.00. New York: Paul B. Hoeber, Inc., Med. Book Dept. of Harper and Bros., 1953.

the cursory way in which the problem of the possible relation of tobacco smoking to cancer is discussed. In the chapters on exfoliative cytology and radiation therapy the authors, probably because of considerations of space, have limited themselves to considerations of the results obtained by these methods. A chapter dealing dispassionately with the results of surgical treatment and of its limitations would make an interesting addition to the book.

This book is, undoubtedly, an important one and fills a real need, for it brings together into convenient form a vast amount of information that is useful to anyone concerned with the problems of tumors, whether they be encountered in the laboratory or on the teaching and research ward. The book will prove invaluable to all who are interested in cancer as a biologic problem of extraordinary interest and intricacy. I trust that the editors will not be unduly disturbed by the minor criticisms that have been made and will keep in mind that they may be of use when the second edition of the book is prepared. I have found the reading of this book a stimulating and rewarding experience and I am certain that others will too. WILLIAM B. WARTMAN.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

DO OXIGENIO NO TRABALHO DE PARTO. By Plinio Tisi Ferraz. 140 pages, 20 illustrations. Rio de Janeiro, 1953.

THE HEPATIC CIRCULATION AND PORTAL HYPERTENSION. By Charles G. Child, III, M.D. 444 pages, 132 illustrations. $12.00. Philadelphia and London: W. B. Saunders Co., 1954.

ACUTE RENAL FAILURE. By Arthur Grollman, Ph.D., M.D., F.A.C.P. 92 pages, 5 illustrations. $4.00. Springfield, Ill.: Charles C Thomas, 1954.

NEUROSURGERY OF INFANCY AND CHILDHOOD. By Franc D. Ingraham, M.D., and Donald D. Matson, M.D. 456 pages, 381 illustrations. $15.00. Springfield, Ill.: Charles C Thomas, 1954.

THE BILLROTH I GASTRIC RESECTION; WITH PARTICULAR REFERENCE TO THE SURGERY OF PEPTIC ULCER. By Horace G. Moore, Jr., M.D., and Henry N. Harkins, M.D., Ph.D., F.A.C.S. 175 pages, 36 illustrations. $7.50. Boston: Little, Brown & Co., 1954.

A MANUAL ON CARDIAC RESUSCITATION. By Robert M. Hosler, M.D., F.A.C.S. 183 pages, 14 illustrations. $4.00. Springfield, Ill.: Charles C Thomas, 1954.

MASTOPATHIE UND MILCHDRUESENKREBS. By Prof. Dr. Georg E. Konjetzny. 140 pages, 48 illustrations. DM 25. Stuttgart: Ferdinand Enke Verlag, 1954.

DIE HALSWIRBELSAEULE; PATHOLOGIE UND KLINIK. By Dr. Med. Gerhard Exner. 140 pages, 42 illustrations. DM 21.60. $5.15. Stuttgart: Georg Thieme Verlag, 1954.

ANATOMY FOR SURGEONS: THE HEAD AND NECK. By W. Henry Hollinshead, Ph.D. Vol. I. 560 pages, 326 illustrations. $10.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1954.

A DOCTOR TALKS TO WOMEN; WHAT THEY SHOULD KNOW ABOUT THE NORMAL FUNCTIONS AND COMMON DISORDERS OF THE FEMALE ORGANS. By Samuel Raynor Meaker, M.D. 231 pages, 12 illustrations. $3.95. New York: Simon & Schuster, 1954.

CARDIOVASCULAR SURGERY. By Gerald H. Pratt, M.D., F.A.C.S. 843 pages, 358 illustrations on 261 figures and 4 color plates. $15.00. Philadelphia: Lea & Febiger, 1954.

ARBEIT UND GESUNDHEIT. Edited by Prof. Dr. phil. et med. M. Bauer and Dr. med. F. Paetzold. Part 52. Orthopaedische Konstruktionen. By Prof. Dr. Franz Schede. 98 pages, 141 iiiustrations. DM 8. Stuttgart: Georg Thieme Verlag, 1953.

MENORRHALGIA—MENSTRUAL DISTRESS. By William Bickers, M.D. 97 pages, 11 illustrations. $2.75. Springfield, Illinois: Charles C Thomas, 1954.

LUNG CANCER. By Seymour M. Farber, M.D. 157 pages, 18 illustrations. $4.75. Springfield, Ill.: Charles C. Thomas, 1954.

CURRENT THERAPY 1954; LATEST APPROVED METHODS OF TREATMENT FOR THE PRACTICING PHYSICIAN. Edited by Howard F. Conn, M.D. 898 pages. $11.00. Philadelphia and London: W. B. Saunders Co., 1954.

MAYO CLINIC DIET MANUAL. By the Committee on Dietetics of the Mayo Clinic. 2nd ed. 247 pages, $5.50. Philadelphia and London: W. B. Saunders Co., 1954.

MANUAL OF CLINICAL MYCOLOGY. By Normal F. Conant, Ph.D., David Tillerson Smith, M.D., Roger Denio Baker, M.D., Jasper Lamar Calloway, M.D., and Donald Stover Martin, M.D. 2nd ed. 456 pages, 202 illustrations. $6.50. Philadelphia and London: W. B. Saunders Co., 1954.

PRATIQUE DE L'HIBERNOTHÉRAPIE; EN CHIRURGIE ET EN MÉDICINE. By H. Laborit and P. Huguenard. 256 pages, 13 figures. 1.400 fr. Paris: Masson & Cie, 1954.

EMBOLIA Y TROMBOSIS. By Th. Naegeli, and P. Matis. 162 pages, 12 illustrations. Barcelona: Folia clinica internacional, 1954.

MODERN MEDICINE ANNUAL 1954. An annual volume containing the articles that appeared in the twenty-four issues of Modern Medicine during 1953. 1454 pages, illustrated. Minneapolis: Modern Medicine, 1954.

KLINISCHE DARMBAKTERIOLOGIE; FUER DIE AERZTLICHE PRAXIS. By Prof. Dr. med. et phil. Tr. Baumgärtel. 132 pages. DM 14.40. $3.40. Stuttgart: Georg Thieme, 1954.

DISEASES OF THE LIVER. By Mitchell A. Spellberg, M.D., F.A.C.P. 646 pages, 92 illustrations. $16.50. New York: Grune & Stratton, Inc., 1954.

THE PAINFUL PHANTOM; PSYCHOLOGY, PHYSIOLOGY, AND TREATMENT. By Lawrence C. Kolb, M.D. 50 pages. $1.50. Springfield, Ill.: Charles C Thomas, 1954.

ATLAS OF ORTHOPEDIC TRACTION PROCEDURES. By Carlo Scuderi, B.S., M.D., M.S., Ph.D. 230 pages, 124 illustrations. $12.50. St. Louis: The C. V. Mosby Co., 1954.

TREASURE-DIVING HOLIDAYS. By Jane and Barney Crile. 263 pages, illustrated. $3.95. New York: The Viking Press, 1954.

AN ATLAS OF CONGENITAL ANOMALIES OF THE HEART AND GREAT VESSELS. By Jesse E. Edwards, Thomas J. Dry, Robert L. Parker, Howard B. Burchell, Earl H. Wood, and Arthur H. Bulbulian. 202 pages, 256 illustrations. $13.50. Springfield, Ill.: Charles C Thomas, 1954.

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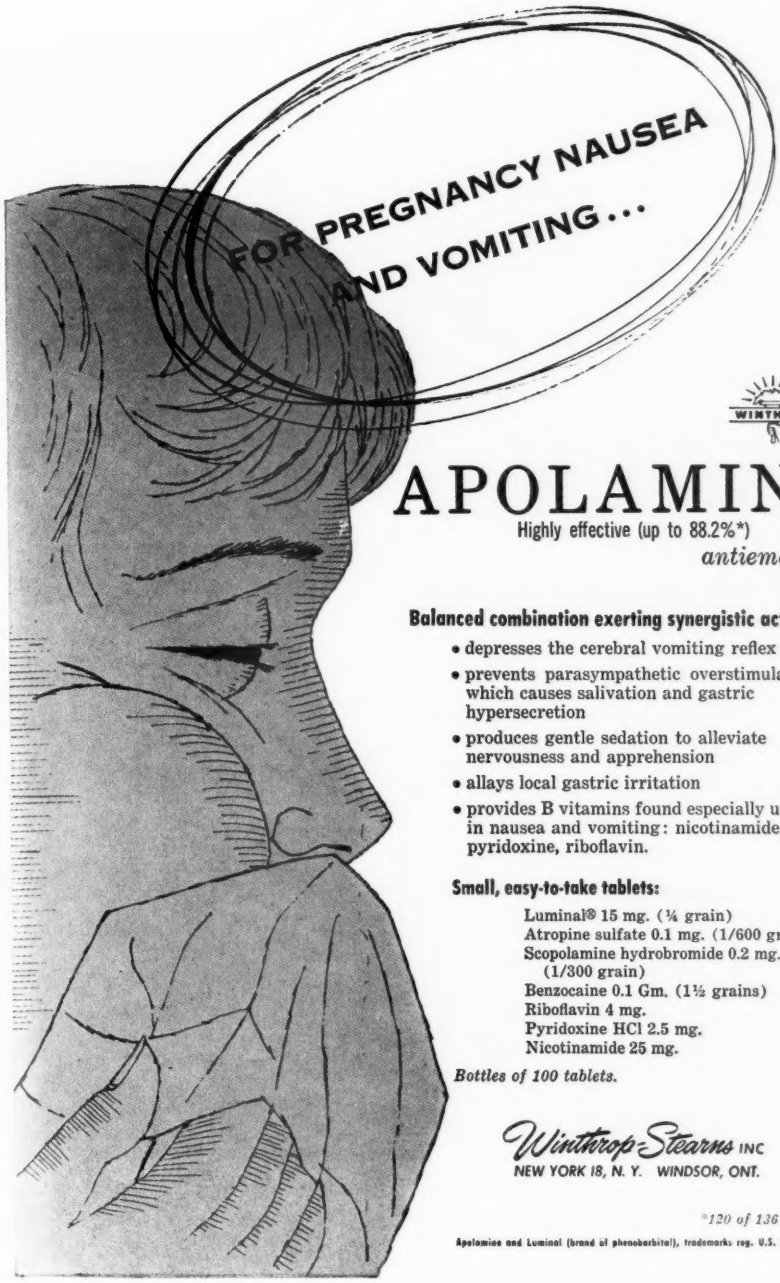

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